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Case Report

Ischemic stroke following varicella vaccine

Gülçin Benbir[a,*], Reza P. Muhammed[a], Zehra I. Hasiloglu[b], Sait Albayram[b] and Cengiz Yalçınkaya[a]
[a]*Department of Neurology, Cerrahpasa Faculty of Medicine, Istanbul University, Istanbul, Turkey*
[b]*Department of Radiology, Cerrahpasa Faculty of Medicine, Istanbul University, Istanbul, Turkey*

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Abstract. Although stroke may develop after varicella zoster virus infection, the relation between varicella vaccine and ischemic stroke is vague. A 13-month-old boy was admitted due to sudden onset right-sided hemiparesis. The past medical and family history were unremarkable, except for the administration of chickenpox vaccine 2 d before. Cranial magnetic resonance imaging showed acute cerebral ischemia. Detailed examinations for the etiological work-up were all normal. A definite causal relationship is difficult to establish between stroke and varicella vaccination, however.post vaccinaton complication may be considered in stroke patients without other demonstrable risk factors.

Keywords: Pediatric stroke, varicella, vaccination

1. Introduction

A stroke may develop after a primary or secondary varicella zoster virus (VZV) infection in children and adults [1,2]. In a recent review of the literature, a total of 70 cases of stroke syndromes were associated with VZV infection [3]. The relation between varicella vaccine and ischemic stroke, on the other hand, is less clear. The US Vaccine Adverse Event Reporting System [4], reported the first case of stroke following varicella vaccinaton in a 4-year-old girl developing hemiparesis weeks after receiving the vaccine, with magnetic resonance imaging (MRI) evidence for cerebral infarctions in the putamen and internal capsule. The second report described two children with acute-onset hemiparesis 5 d and 3 wk following varicella vaccination [5], though they had co morbidities such as a patent foramen ovale and severe iron-deficiency anemia. In a retrospective population-based cohort study evaluating the association between varicella vaccination and ischemic stroke [6], there was no temporal clustering for post-vaccine stroke cases, and the adjusted hazard ratio was not elevated concluding that there was no association between varicella vaccine and stroke. However, a close temporal relationship with the vaccination and ischemic stroke in a patient without any other identifiable risk factors should question the causal association. Here we report a boy with acute-onset hemiparesis 2 d after varicella vaccination.

2. Case report

A 13-month-old boy was admitted to the hospital due to right-sided hemiparesis of sudden onset. While playing with his toys, he dropped the toy he was holding with his right hand. When the mother held the child, she noticed weakness in his right arm and leg.

On neurological examination, the patient had a right-sided hemiparesis with muscle strength of 4/5, with hyperreflexia and extensor Babinski sign on the right.

*Corresponding author: Gülçin Benbir, Department of Neurology, Istanbul University Cerrahpasa Faculty of Medicine, Istanbul, Turkiye. Tel.: +90 533 226 3797; Fax: +90 212 632 9696; E-mail: drgulcinbenbir@yahoo.com.

The sensory examination for pain was normal. There was no clonus. The patient's head circumference, body height and weight were within normal percentiles. The patient was born via caesarian section due to preeclampsia at the 34th week of gestation as the first child from the first gestation born to non-consanguineous parents. He was hospitalized in the intensive care unit for one week and discharged without any complications. His developmental milestones were normal. The parents stated that the child had vaccines regularly, and had the chickenpox vaccine (Oka strains, attenuated alive vaccine, 1000 50% tissue culture infective dose/dose-0.5 mL) 2 d before. He had no contact with a patient with varicella. His other vaccines included Bacillus Calmette-Guérin at 2 mo, hepatitis B and diphtheria-pertussis at 2 and 6 mo, polio and rotavirus vaccine at 2, 4 and 6 mo, pneumococcus at 4, 6 and 8 mo, tetanus at 6 mo, and measles-mumps-rubella vaccine at 12 mo. The varicella vaccine (not combined with measles-mumps-rubella) was administered at 13 mo without any other additional vaccines. The family history was unremarkable, except that his mother had zinc deficiency, for which she was on supplementary medications during the pregnancy.

Cranial computerized tomography showed a hypodense lesion in the periventricular deep white matter next to the corpus of the left lateral ventricle (Fig. 1A). Cranial MRI demonstrated a hypointense lesion in T1-weighted images and a hyperintense lesion in T2-weighted and fluid attenuated inversion recovery images (Fig. 1B). The intracranial and extra cranial magnetic resonance angiography (MRA) was normal (Figs. 2A and 2B).

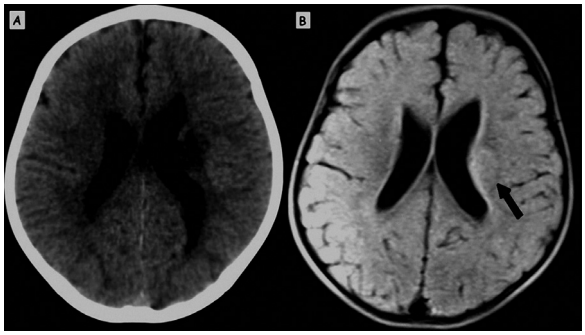

Fig. 1. Hypodense lesion in the periventricular deep white matter next to the corpus of the left lateral ventricle in cranial computerized tomography (A); and hyperintense lesion (black arrow) in the periventricular deep white matter adjacent to the left lateral ventricle on axial fluid attenuated inversion recovery magnetic resonance imaging (B).

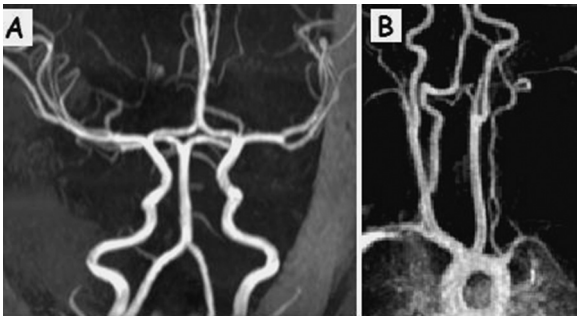

Fig. 2. Normal intracranial (A) and extracranial (B) magnetic resonance angiography images.

The echocardiography was normal. The amino and organic acid analysis in the blood and urine was normal, as well as plasma chromatography. Routine blood tests including whole blood count, peripheral smear, antinuclear antibody and anti-double-stranded DNA antibody levels, anti-cardiolipin antibodies (immunoglobulin G/M), homocysteine level, hemoglobin subtypes (A1/A2/F/S), protein S and C levels, anti-thrombin III activity and factor VIII activity were all normal. The mutation analysis for methylenetetrahydrofolate reductase, factor V (G1691A, Leiden) and prothrombin (G20210A) were negative. The electroencephalography was normal. The known risk factors and triggering conditions such as other infections, drugs, trauma or invasive interventions were all excluded.

The patient was diagnosed to have an ischemic infarction, and acetylsalicylic acid was started. On his last follow-up examination 3 wk after the event, his neurological examination was normal. A control cranial MRI showed the ischemic lesion at late subacute-chronic stage (Fig. 3).

3. Discussion

We present the case of a 13 month old diagnosed to have an ischemic stroke associated with the administration of a varicella vaccination. He had no risk factors for ischemic stroke, and despite a detailed work-up, no etiology was identified. Because there are only few case reports in the literature either without a detailed work-up or with other co morbidities [4,5], there is debate about the association between varicella vaccination as the cause of the stroke. Moreover, a population-based study could not find an increased hazard ratio for stroke following vaccination, which was a retrospective study performed in a selected population, by searching the

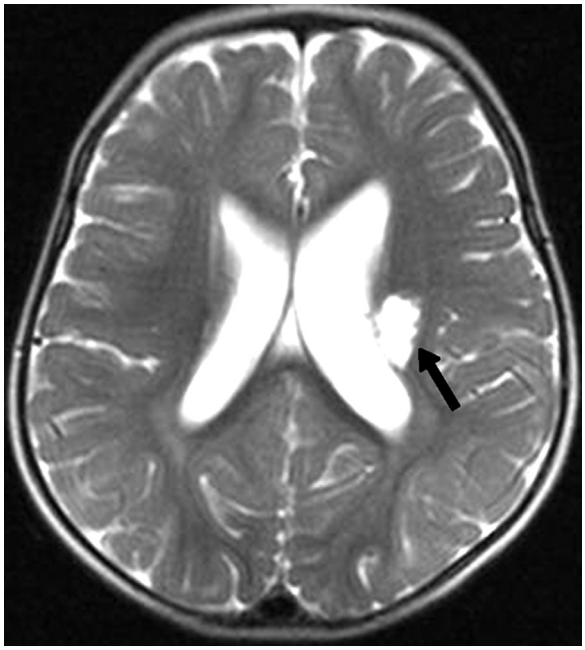

Fig. 3. Late subacute-chronic infarction (black arrow) on axial T2-weighted magnetic resonance imaging after 3 wk.

computerized data for first-ever inpatient cases [6]. Although the etiology remains unknown in about one-third of stroke cases in children and young adults [7], a close temporal relationship with the vaccination and ischemic stroke in a patient without any other identifiable risk factors should question the possible causal association in the presented patient.

The infarction of our patient was localized in the periventricular deep white matter adjacent to the left lateral ventricle. This location was commonly reported in stroke following varicella infection [3]. Also, our patient had a normal MRA, which is the case in about one fifth of ischemic stroke patients following primary infection [3]. In a recent study [8], 40 children with arterial ischemic stroke and normal MRA were identified, and 50% of them had infarction confined to the lenticulostriate branches of the middle cerebral artery. The authors concluded that these children were not a distinct demographic group, but more likely to have single-territory lesions with nonvascular risk factors. The stroke mechanism in children with normal MRA remains unclear.

The pathogenesis of arterial ischemic stroke following varicella infection is proposed to result from a non-cytolytic infection of smooth muscle cells in the media and functional damage of the vascular endothelium [1,9]. VZV vasculopathy is mainly thought to result from direct infection of the vessels with varicella; but it could also result from a post viral immune-mediated reaction [10]. On this basis, it could be speculated that the same mechanism may also be responsible for stroke following varicella vaccine, as it contains live attenuated virus [11]. The vaccination may also trigger the genetic predisposition or underlying risk factors for stroke, demonstrated or not. We believe that the latter explanation is the case in our patient, as the possibility of an autoimmune reaction is unlikely to develop only 2 d after vaccination. The interval between stroke and varicella infection or vaccination could also be questioned. The median interval following varicella vaccination was reported as 18 wk in a meta-analysis by Ciccone et al. [3], while a patient with stroke 24 h after typical varicella exanthema was also present. Stroke following varicella vaccination, on the other hand, was described at least 5 d after the vaccination [5].

In conclusion, although a definite causal relationship is difficult to establish, the varicella vaccination is the only risk factor in the presented patient without any other demonstrable risk factors. The aim of this report is not to disregard the vast beneficial value of the varicella vaccination [12], but rather to query a rare complication of the live attenuated vaccination or VZV.

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