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Ischemic stroke associated with adenoviral infection in a 4-year-old boy

Marko Kutleša[1], Goran Tešović[1], Ivica Knezović[1], Branko Miše[1], Klaudija Višković[2], Nina Barišić[3]

[1]Department of Pediatric Infectious Diseases, University Hospital for Infectious Diseases "Dr. Fran Mihaljević", Zagreb, Croatia
[2]Department of Radiology, University Hospital for Infectious Diseases "Dr. Fran Mihaljević", Zagreb, Croatia
[3]Department of Neuropediatrics, University Hospital Center of Zagreb Medical School, Zagreb, Croatia

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Ischämischer Schlaganfall in Verbindung mit einer Adenovirus-Infektion bei einem 4-jährigen Knaben

Zusammenfassung. Wir stellen einen Fall eines arteriellen ischämischen Schlaganfalls bei einem 4 Jahre alten – vorher völlig gesunden – Knaben mit nachgewiesener Adenovirus-Infektion des oberen Respirationstrakts vor.

Eine adenovirale Meningitis und Enzephalitis wurde wiederholt beschrieben, was für die Fähigkeit der Neuroinvasion der Adenoviren spricht. Ein Zusammenhang zwischen einer Adenovirus-Infektion und einem arteriellen ischämischen Schlaganfall wurde allerdings bis jetzt noch nicht beschrieben. Als einzige Mikroorganismen wurden HIV und Varizella Zoster-Viren mit einem ischämischen Schlaganfall in Abwesenheit einer akuten Infektion des ZNS in Zusammenhang gebracht. Bei Patienten mit einer HIV-Infektion kann der ischämische Insult durch eine Vaskulitis und eine Hyperkoagulabilität verursacht sein. Eine granulomatöse Arteritis der Gefäßwand ist die Ursache für einen Post-Varizellen-Gehirninfarkt beziehungsweise für einen ischämischen Insult nach einer Infektion mit Herpes Zoster ophthalmicus.

Wir glauben, dass bei unserem Patienten ein Mechanismus wie beim Post-Varizellen-Gehirninfarkt mit einer Ausbreitung der Adenoviren über den ophthalmischen Ast des N. trigeminus auf die befallene arterielle Gefäßwand stattgefunden hat. Adenoviren sind neuroinvasiv – die Conjunktivitis könnte das Virus in Kontakt mit dem N. ophthalmicus gebracht haben. Konsekutiv könnte dann die Stenose der Arterie durch die von den Adenoviren ausgelöste lokale Entzündung verursacht worden sein.

Auf Grund unserer Erfahrung empfehlen wir, bei allen vorher gesunden Kindern mit Fieber und einer mit einem ischämischen Insult kompatiblen Klinik eine prompte Untersuchung auf Infektion mit Adenoviren durchzuführen. Eine möglichst frühe Diagnose und Therapie könnte den Verlauf der Erkrankung verbessern und die neurologische Erholung beschleunigen.

Summary. We present a case of childhood arterial ischemic stroke associated with proven adenoviral upper respiratory tract infection in a previously healthy 4-year-old boy. Adenoviral meningitis and encephalitis have been reported repeatedly, thus confirming the neuroinvasive capability of these viruses. However, an association between adenoviral infection and arterial ischemic stroke has not been described thus far. HIV and varicella zoster virus are the only microorganisms that have been consistently associated with arterial ischemic stroke in the absence of acute central nervous system infection. In HIV-infected individuals ischemic stroke can be caused by vasculitis and hypercoagulability. Granulomatous arteritis of the vessel wall causes post-varicella cerebral infarction and ischemic stroke after herpes zoster ophthalmicus. We suggest that in our patient a post-varicella cerebral infarction-like mechanism of adenoviral spread to the affected artery wall occurred through the ophthalmic branch of the trigeminal nerve. Adenoviruses are neuroinvasive and inflamed conjunctiva might have permitted introduction of the virus into ophthalmic nerve tissue. In consequence, the stenotic lesion of the artery might have been induced by the presence of adenovirus and the subsequent inflammatory reaction. We recommend a prompt quest for adenoviral infection in all previously healthy children with fever and clinical presentation compatible with ischemic stroke, because timely diagnosis and treatment could improve the outcome and hasten neurological recovery.

Key words: Adenovirus, ischemic stroke, infection, direct immunofluorescent antibody test.

Correspondence: Marko Kutleša, M.D., Department of Pediatric Infectious diseases, University Hospital for Infectious Diseases "Dr. Fran Mihaljević", Mirogojska 8, 10000 Zagreb, Croatia, E-mail: kutlesam@yahoo.com

Introduction

Adenoviruses are DNA viruses well known for their propensity to cause respiratory and gastrointestinal tract infections. Rarely, they can cause viremia and disseminated disease, mostly in neonates or otherwise immunocompromised individuals [1]. In recipients of solid-organ transplants, acute hemorrhagic cystitis is an additional adenoviral entity [2]. Meningitis and encephalitis have been reported repeatedly, thus confirming the neuroinvasive capability of adenoviruses [3]. However, an association between adenoviral infection and ischemic stroke has not been described thus far.

Ischemic stroke is a rare event during childhood and a specific etiology can be identified in only approximately 50% of the cases [4]. Unsurprisingly, ischemic stroke in children, where atherosclerosis is not an issue, has a different etiology than in the adult population. Congenital and acquired heart problems, hematologic conditions, vasculopathies, metabolic disorders and drug ingestion are the most common etiologies of childhood stroke and are beyond the scope of this report [5, 6].

It is well known that bacterial meningitis, mycoplasma, syphilis, central nervous system (CNS) tuberculosis, fungi, and viral infections including HIV and varicella can induce ischemic stroke through assumed secondary vasculitis [7]. Some respiratory infections, not of adenoviral etiology, have recently been associated with ischemic stroke [8]. Ischemic stroke occurring during concomitant enteroviral meningitis, influenza A and parvovirus B19 infection has been reported [9–11]. HIV and varicella zoster virus are the only microorganisms that have been consistently associated with ischemic stroke in the absence of acute CNS infection. In HIV-infected individuals, apart from atherosclerosis, ischemic stroke can be caused by vasculitis and hypercoagulability [12]. Granulomatous arteritis of the vessel wall causes post-varicella cerebral infarction (PVCI) and stroke after herpes zoster ophthalmicus [13]. Basilar artery aneurysms have also been reported after varicella infections [14].

We present a case of ischemic stroke associated with proven adenoviral upper respiratory tract infection in a previously healthy 4-year-old child.

Case presentation

A 4-year-old white boy with suspected meningoencephalitis was admitted to the pediatric department of the University Hospital for Infectious Diseases, Zagreb, in October 2008. He had been treated in another hospital for one day before admission. Acute disease had commenced five days previously, with fever, nasal congestion, conjunctivitis, sore throat, cough and malaise. Right-sided hemiparesis with aphasia occurred on the fourth day of the acute respiratory infection. Limb weakness progressed to plegia within 24 hours. Central facial palsy on the right side became evident one day after neurological symptoms had begun. Head trauma was not registered. On admission the boy was alert and febrile. Tonsillar enlargement with erythema and subtle exudate was present. Purulent nasal discharge was visible and anterior cervical lymph nodes were enlarged and tender. Otoscopic examination was normal. Meningeal signs were negative. Neurological examination revealed right-sided flaccid hemiplegia and ipsilateral central facial palsy. The boy suffered from motoric aphasia: he was able to comprehend words and sentences but was not able to speak. Tendon reflexes were diminished on the afflicted side with evident extensor plantar response. The remaining physical examination was unremarkable.

The child was the result of the mother's second pregnancy, which had been complicated with premature uterine contractions at 32 weeks. Tocolysis was indicated for the remaining period of pregnancy. A healthy child was delivered by scheduled cesarean section after 39 weeks of gestation and his health remained stable throughout the newborn period. The rest of the medical history revealed only surgical repair of a left-sided inguinal hernia at 2 months of age. The child had met all developmental milestones at the appropriate age. Childhood diseases including varicella were not recorded in the medical history.

The white blood cell count revealed leukocytosis of 19.6×10^9/l (normal range $4–10\times10^9$/l) with normal differential. The platelet count was 395×10^9/l (normal range $140–400\times10^9$/l) and hemoglobin level 13.3 g/dl (normal range 12.0–14.0 g/dl). C-reactive protein was 2.6 mmol/l (normal range <10.0 mmol/l) and erythrocyte sedimentation rate 20 mm/h (normal range 0–15 mm/h). Urine analysis was normal. Blood urea nitrogen, sodium, potassium, calcium, phosphorus, aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase and creatine kinase were within normal range. Acid-base analysis, prothrombin time, activated partial thromboplastin time, thrombin time, D-dimer assay, antithrombin III and fibrinogen were also within normal limits. Antineutrophil cytoplasmic antibodies were negative.

Chest radiography and electrocardiogram showed no abnormalities. Transthoracic echocardiogram showed a structurally normal heart without thrombi. Lumbar puncture yielded colorless cerebrospinal fluid (CSF) with two leukocytes per cubic millimeter and normal levels of glucose and protein. Electroencephalogram detected focal slowing above the left frontal and parietal areas. A computed tomography scan of the brain without contrast performed at another hospital and prior to the lumbar puncture detected no abnormalities. Blood, urine and CSF cultures were sterile and throat culture was negative for group A streptococcus.

Polymerase chain reaction of the CSF did not detect herpes simplex virus, enterovirus or *Listeria monocytogenes*. In ELISAs of the serum and CSF, antibodies against varicella zoster virus, *Mycoplasma pneumoniae, Chlamydophila pneumoniae, Borrelia burgdorferi, Bartonella henselae* and central European tickborne encephalitis were not detected. Epstein–Barr virus, cytomegalovirus and adenoviral antibodies were present only in the serum and indicated past infection.

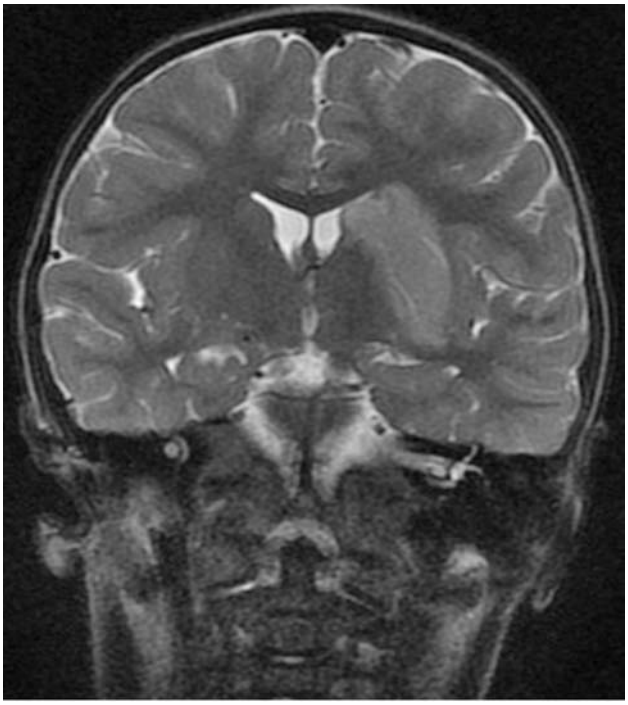

Fig. 1. Coronal T2-weighted MR image shows a focus of high signal intensity in the left-sided basal ganglia and internal capsule area compatible with infarcted tissue in the territory supplied by the lenticulostriate arteries

Direct immunofluorescent antibody tests of nasopharyngeal aspirate were positive for adenoviral antigen and negative for respiratory syncytial and parainfluenza viral antigens. Five days after the initial symptoms of ischemic stroke had begun magnetic resonance imaging (MRI) without contrast was performed at another hospital. A T2-weighted MRI scan revealed a left-sided hyperintense lesion compatible with ischemic stroke in the basal ganglia and internal capsule area (Fig. 1). The size of the lesion was 33 × 21 mm and the distribution was typical of ischemia of the lenticulostriate arteries. Follow-up MRI three weeks later was consistent with subacute ischemia of the same area.

After exclusion of CNS infection and MRI confirmation of the ischemic stroke, low-molecular-weight heparin and corticosteroid therapy were started before the patient was transferred to the pediatric neurology ward of another clinical hospital. Symptoms of acute respiratory infection spontaneously resolved before the discharge from our hospital. However, neurological deficits remained unchanged at that time. Corticosteroid therapy continued for five days at another hospital with gradual tapering afterwards. The boy received low-molecular-weight heparin therapy for three months.

Early follow-up a month after the ischemic stroke revealed spastic monoparesis of the right leg and plegia of the right arm. He was able to walk with assistance. The boy's motoric aphasia resolved and his speaking abilities returned to the same level as they were prior to his current illness.

Discussion

We report a case of ischemic stroke associated with adenoviral upper respiratory tract infection in a 4-year-old boy. The typical clinical presentation of adenoviral infection was confirmed with a direct immunofluorescent antibody test of nasopharyngeal aspirate that has specificity of nearly 100% [15]. Ischemic stroke was confirmed by MRI of the brain. Digital subtraction arteriography was not available to us at the time. Angiography was not performed during the initial MRI and was technically insufficient on the repeat MRI scan. However, dynamics of the lesion revealed by the MRI clearly indicated ischemic stroke. Unfortunately, adenoviral typing and polymerase chain reaction of adenoviral genetic material could not be performed. Diagnostic work-up did not detect other microorganisms as possible etiologic agents of the boy's acute infection or confirm some other cause for the ischemic stroke, including hypercoagulability or thromboembolic incident.

Certainly, the association between ischemic stroke and adenoviral infection in our patient could be purely coincidental. However, since the neuroinvasive capability of adenoviruses is well established, secondary vasculitis as in post-varicella cerebral infarction (PVCI) is quite possible [3]. In the latter scenario several possible pathogenetic cascades leading to ischemic stroke could be argued. One scenario implies adenoviral viremia and vessel-wall inflammation induced by the presence of circulating virus. A second potential sequence of events could be entrance of the virus into the CNS during viremia and focal inflammation of the artery afflicted, but without presence of meningitis. As a third scenario, adenoviral-triggered autoimmunity could have been responsible for the child's stroke.

Interestingly, all of the pathogenetic mechanisms described above imply a focal pathological process in the vessel wall during a systemic response, whether infective or autoimmune. In our view it seems unlikely that a focal vessel inflammation was induced by a systemic reaction to any etiology. We suggest that an acute PVCI-like mechanism of adenoviral spread to the affected artery wall via the ophthalmic branch of the trigeminal nerve is justifiably arguable. Adenoviruses are neuroinvasive and inflamed conjunctiva might have permitted introduction of the virus into the ophthalmic nerve tissue. Consequently, the stenotic lesion in the affected artery might have been induced by the presence of adenovirus and the subsequent inflammatory reaction. Furthermore, MRI confirmed that the brain area afflicted with ischemic stroke in our patient was analogous to the areas involved in reported patients with PVCI [13]. The morphology of the ischemic stroke thus provides additional argument for the proposed pathogenesis in our patient.

Although the suggested pathogenetic sequence of events lacks irrefutable evidence, it is plausible. Therefore, regardless of the pathogenetic mechanism and limited experience, the use of antiviral agent in patients with ischemic stroke and proven adenoviral infection seems prudent. Cidofovir has been repeatedly found to

have superior efficacy in treatment of severe adenoviral infections [16, 17]. Regrettably, it was not available to us at that time and our patient was deprived of specific antiviral therapy. Anti-inflammatory treatment alongside antiviral therapy should also be considered, because of the probable inflammation as a part of the disease pathogenesis. Moreover, implementation of antithrombotic therapy is part of the usual treatment in ischemic stroke, regardless of the etiology.

Conclusion

Even on the basis of very limited experience we recommend a prompt quest for adenoviral infection in all previously healthy children with fever and clinical presentation compatible with acute ischemic stroke, because timely diagnosis and treatment could improve the outcome and hasten neurological recovery.

Conflict of Interest
The authors declare that there is no conflict of interest.

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