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Arterial ischemic stroke associated with adenoviral infection in a 4-year old

RUNNING HEAD: Arterial ischemic stroke and adenoviral infection

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Abstract

We present a case of childhood arterial ischemic stroke in previously healthy 4-year old boy associated with proven adenoviral upper respiratory tract infection. Adenoviral meningitis and encephalitis have been reported repeatedly thus confirming their neuroinvasiveness. However, 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 besides from atherosclerosis, arterial ischemic stroke can be caused by vasculitis and hypercoagulability. Granulomatous arteritis of the vessel wall causes post-varicella cerebral infarction and arterial ischemic stroke after herpes zoster ophthalmicus. It could be suggested that 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 introduced the virus to the ophthalmic nerve tissue. Consequently, the stenotic lesion of the artery affected might have been induced by the presence of adenovirus and subsequent inflammatory reaction. Even on the basis of very limited experience we can recommend a prompt quest for adenoviral infection in all previously healthy children with fever and clinical presentation compatible with arterial 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

Introduction

Adenoviruses are DNA viruses well known for their propensity to cause respiratory and gastrointestinal tract infections. Scarcely, they can cause viremia and disseminated disease, mostly in neonates or otherwise imunocompromised individuals [1]. In solid organ transplant recipients additional adenoviral entity known is acute hemorrhagic cystitis [2]. Meningitis and encephalitis have been reported repeatedly thus confirming adenoviral neuroinvasiveness [3]. However, association between adenoviral infection and arterial ischemic stroke (AIS) has not been described thus far.

AIS is a rare event during childhood and specific etiology can be determined in approximately 50% of the cases [4]. Expectedly, in children AIS has different etiology than in adult population without atherosclerosis as an issue. Congenital and acquired heart problems, hematologic conditions, vasculopathies, metabolic disorders and drug ingestion are the most common etiologies of childhood AIS, those are beyond the scope of this report [5,6].

It is well known that bacterial meningitis, mycoplasma, viral infections including HIV and varicella, syphilis, central nervous system tuberculosis and fungi can induce AIS through assumed secondary vasculitis [7]. Some respiratory infections, not of adenoviral etiology, have recently been associated with AIS [8]. AIS occurring during concomitant enteroviral meningitis, Influenza A and parvovirus B 19 infection have been reported [9,10,11]. HIV and varicella zoster virus (VZV) are the only microorganisms that have been consistently associated with AIS in the absence of acute central nervous system (CNS) infection. In HIV infected individuals besides from atherosclerosis, AIS can be caused by vasculitis and hypercoagulability [12]. Granulomatous arteritis of the vessel wall causes post-varicella cerebral infarction (PVCI) and AIS after herpes zoster ophthalmicus [13]. Basilar artery aneurysm was also reported after varicella [14].

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

Case report

A 4-year old white boy was admitted to the Department of Pediatric Infectious diseases of the University Hospital for Infectious diseases in October of 2008 for suspected meningoencephalitis. He was treated in another hospital for one day before the transfer to our hospital. Acute disease commenced five days prior to admission with fever, nasal congestion, conjunctivitis, sore throat, cough and malaise. Right-sided hemiparesis with aphasia occurred on the fourth day of 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 begun. Head trauma was not registered. At 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 and 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. Remaining physical examination was unremarkable.

The child was born after mother's second pregnancy complicated with premature uterine contractions at 32 weeks. Tocolysis was indicated for the remaining period of pregnancy. Healthy neonate was delivered after 39 weeks of gestation with scheduled cesarean section and his health remained stable throughout the newborn period. Rest of the medical history revealed only surgical repair of the left-sided inguinal hernia at 2 months of age. He had met all developmental milestones at the appropriate age. Childhood diseases including varicella were not registered.

Laboratory examination revealed leukocytosis of 19.6×10^9/L (normal range 4-10 $\times$ 10^9/L) in white blood cell count with normal differential, platelet count was 395×10^9/L (normal

range 140-400 × 10^9/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, aspartat 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 within normal limits as well. Antineutrophil cytoplasmic antibodies were negative. Chest radiography and electrocardiogram showed no abnormalities. Transthoracic echocardiogram showed 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. Computed tomography scan of the brain without contrast preformed 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 failed to detect herpes simplex virus, enterovirus and *Listeria monocytogenes*. On the enzyme linked immunoassay of the serum and CSF, antibodies for VZV, *Mycoplasma pneumoniae, Chlamydophila pneumoniae*, *Borrelia burgdorferi, Bartonella henselae* and central european tick-borne encephalitis were not detected. Epstein-Barr virus, cytomegalovirus and adenoviral antibodies were present only in serum and indicated past infection.

Direct immunofluorescent antibody test (DFA) of nasopharyngeal aspirate was positive for adenoviral and negative for respiratory syncytial and parainfluenza viral antigen. Five days after initial symptoms of AIS begun, magnetic resonance imaging (MRI) without contrast was performed at another hospital. T2-weighted (Fig. 1) revealed a left-sided hyperintense lesion compatible with ischemic stroke in the basal ganglia and internal capsule area. The size of the lesion was 33x21 millimeter and the distribution was typical of lenticulostriate arteries ischemia.

Follow up MRI performed three weeks afterwards was consistent with subacute ischemia of the same area.

After exclusion of the CNS infection and MRI confirmation of the AIS 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 four months.

Early follow up a month after AIS occurred revealed spastic monoparesis of the right leg and plegia of the right arm, with assistance he was able to walk. The boy's motoric aphasia resolved and his speaking abilities are at the same level as they were prior to his current illness.

Discussion

We report a case of AIS in a 4 year old boy associated with adenoviral upper respiratory tract infection. Typical clinical presentation of adenoviral infection was confirmed with direct immunofluorescent antibody test of nasopharyngeal aspirate that has specificity of nearly 100% [15]. AIS was ratified by MRI of the brain. Unfortunately, adenoviral typing and polymerase chain reaction of adenoviral genetic material could not be performed. Unfortunately, digital subtraction angiography was not performed since it was not readily available and MR angiography was technically inadequate and thus not interpretable. Diagnostic work-up failed to detect other microorganisms as possible etiologic agents of the boy's acute infection or to confirm some other cause for the AIS, including hypercoagulability or thromboembolic incident.

Naturally, the association between AIS and adenoviral infection in our patient could be purely accidental. However, since neuroinvasiveness of adenoviruses is well established, secondary vasculitis as in PVCI is quite possible [3]. In latter scenario several possible pathogenetic cascades leading to AIS could be argued. One scenario implies adenoviral viremia and the vessel wall inflammation induced by the presence of the virus in circulation. Second sequence of events alludes the entrance of the virus to the CNS during viremia and focal inflammation of the artery afflicted, but without presence of meningitis. Finally, adenoviral triggered autoimmunity might have been responsible for our patient's AIS as well.

Interestingly, all of the pathogenetic mechanisms described previously imply focal pathological process in the vessel wall during a systemic response, infective or autoimmune. In our view it seems unlikely that a focal vessel inflammation was induced by a systemic reaction of any etiology. Thence, we infer that acute PVCI like mechanism of adenoviral spread to the affected artery wall via ophthalmic branch of the trigeminal nerve is justifiably arguable. Adenoviruses are neuroinvasive and inflamed conjunctiva might have introduced the virus to the ophthalmic nerve tissue. Consequently, the stenotic lesion of the artery affected might have been

induced by the presence of adenovirus and subsequent inflammatory reaction. Furthermore, magnetic resonance imaging confirmed that the brain area afflicted with AIS in our patient was analogous to the areas involved in reported PVCI patients [13]. Thence, the morphology of the AIS provides additional argument for the proposed pathogenesis in our patient.

Although suggested pathogenetic sequence of events lacks irrefutable evidence it is plausible. Therefore, regardless of the pathogenetic mechanism and insufficient experience, the utilization of the anti-viral agent in patients with AIS and proven adenoviral infection seems prudent. Cidofovir is the agent found to have superior efficacy in treatment of severe adenoviral infections on repeated occasions [16,17]. Regrettably, it was unattainable to us at the time, and our patient was deprived of the specific anti-viral therapy. Due to the probable inflammation as a part of the disease pathogenesis anti-inflammatory treatment alongside anti-viral therapy should be considered. Implementation of anti-thrombotic therapy is a part of the usual treatment approach in AIS, regardless of the etiology.

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

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Abbreviations

AIS - arterial ischemic stroke

PVCI - post-varicella cerebral infarction

Figure 1. *Coronal T2 weighted MR image showes a focus of high signal intenisiy in left sided basal ganglia and internal capsule area compatible with infarcted tissue on the teritory supplied by the lenticulostriate arteries*