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Case Report

Rhinovirus-associated acute encephalitis/encephalopathy and cerebellitis

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Abstract

Background: Rhinovirus is a common respiratory pathogen for children throughout the year; nevertheless, its central nervous system involvement is extremely rare, and only two cases have been reported to date: meningitis and sepsis-like illness.

Patient: A previously healthy 2-year-old Japanese boy developed fever, followed by seizures and lethargy. His cerebrospinal fluid cell count and protein level were slightly increased; brain magnetic resonance imaging showed abnormal intensities in the bilateral cerebellar dentate nuclei, which were prominent in diffusion-weighted images. After his consciousness disturbance improved, cerebellar dysfunction became apparent. He was treated symptomatically, without steroids or any other immunosuppressants. He almost recovered within a few months; however, cerebellar atrophy became evident on brain magnetic resonance imaging. Using acute specimens, human rhinovirus A was detected in his throat swab and cerebrospinal fluid.

Discussion: Acute cerebellitis, in which cerebellar inflammation is predominant, is occasionally accompanied by cerebral symptoms, such as consciousness disturbance and seizures. As a causative pathogen, rotavirus is the most common; however, rhinovirus-associated acute encephalitis/encephalopathy and concurrent cerebellitis have not been reported before. Further research, using recent molecular techniques to detect various central nervous system pathogens, including rhinovirus, is needed to delineate the underlying pathophysiology.

Keywords: Rhinovirus; Encephalitis; Encephalopathy; Cerebellitis; Dentate nuclei

1. Introduction

Rhinovirus, divided into three species (A–C), is prevalent in Japanese children throughout the year (detected in 192 out of 512 nasal aspirate samples from symptomatic children [37.5%]), causing various respiratory symptoms; asymptomatic carriers also exist (detected in 20 out of 200 throat gargle samples from asymptomatic children [10.0%]) [1,2]. Nevertheless, its central nervous system (CNS) involvement is extremely rare, and only two cases have been reported worldwide [3,4].

Herein, we report the first case of rhinovirus-associated acute encephalitis/encephalopathy and concurrent cerebellitis.

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2. Case report

A previously healthy 2-year-old Japanese boy developed fever; this day was designated as day of illness (DOI) 0. On DOI 1, he appeared inactive and experienced a brief convulsion. On DOI 2, shortly after midnight, he experienced another convulsion and was admitted to our hospital. On admission, his body temperature was 37.8 °C. Rapid antigen detection test for group A streptococcus, using throat swab, was positive. The blood analysis revealed no abnormalities, except for increased C-reactive protein levels (17.82 mg/dl) and peripheral white blood cell count (16,100/μl [80.3% neutrophils]). We initially diagnosed him with streptococcal pharyngitis and febrile seizures, and began to administer ampicillin. Later that day (DOI 2), he showed lethargy and neck stiffness. Brain computed tomography showed normal result, except a left middle cranial fossa arachnoid cyst. The cerebrospinal fluid cell count and protein levels were slightly increased (202 cells/μl [polymorphonuclear cells, 181/μl] and 48 mg/dl, respectively), while the glucose level was normal (74 mg/dl) and Gram staining was negative. Under the consideration of bacterial meningitis and herpes simplex encephalitis, we changed the antibiotics to meropenem and ceftriaxone, and then added acyclovir; later, the results of bacterial cultures of his blood and cerebrospinal fluid, and herpes simplex virus nucleic acid amplification performed using polymerase chain reaction (PCR) of his cerebrospinal fluid sample, were all found negative. On DOI 3, his lethargy persisted, and electroencephalography showed bilateral occipital-parietal dominant 200–300 μV delta-theta waves while he seemed awake, and humps and spindles while he seemed asleep, without any paroxysms. On DOI 4, brain magnetic resonance imaging (MRI) showed abnormal intensities in the bilateral cerebellar dentate nuclei, which were prominent in diffusion-weighted images (DWI) (Fig. 1D–F), without any accompanying cerebral abnormality (Fig. 1A–C). On DOI 6, sleep electroencephalography showed no abnormality. Without any specific treatments, such as steroid or any other immune suppressants, his consciousness had been improving gradually, and was almost back to normal till DOI 10; nonetheless, he could not speak or sit without assistance, exhibiting decreased muscle tone. On DOI 10, brain MRI, including T1- and T2-weighted and fluid-attenuated inversion recovery imaging, did not show any abnormality. During the MRI session, he awoke earlier than expected; therefore, DWI were not obtained. On discharge (DOI 18), he could speak two-word sentences in a slow and dysarthric manner, briefly sit without assistance, crawl, and stand with assistance. On DOI 26, he could walk without assistance in a wide-based manner. On DOI 135, brain MRI showed cerebellar atrophy (Fig. 1G–I). On DOI 143, the Kyoto Scale of Psychological Development (2001) (http://www.kiswec.com/), a widely used developmental test in Japan, showed his overall developmental quotient (DQ) to be 87, with three subdomains: postural-motor DQ, 74; cognitive-adaptive DQ, 89; and language-social DQ, 87.

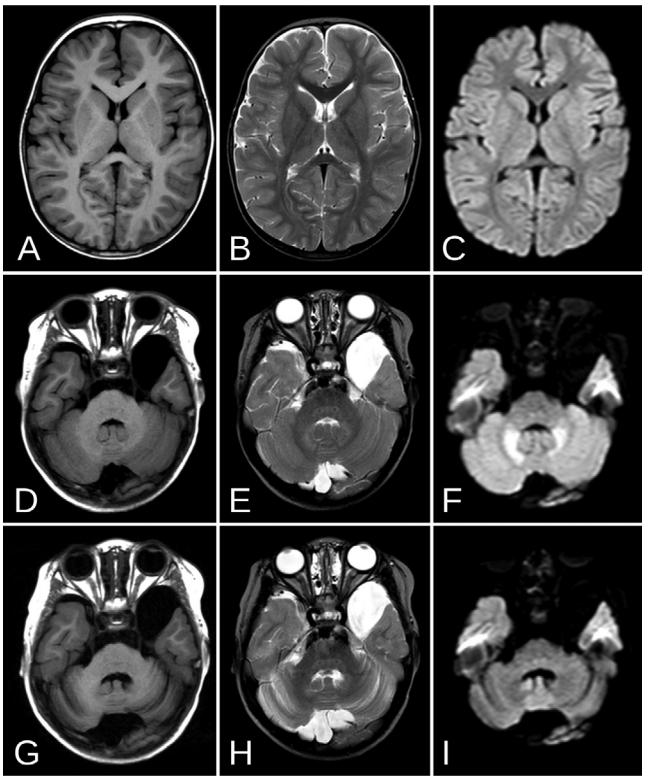

Fig. 1. Magnetic resonance findings of our patient on day of illness (DOI) 4 (A–F) and DOI 135 (G–I): left column, T1-weighted images (A, D, and G); middle column, T2-weighted images (B, E, and H); and right column, diffusion-weighted images (C, F, and I). On DOI 4, cerebral images (A–C) do not show any abnormality; however, cerebellar images (D–F) show abnormal intensities in the bilateral cerebellar nuclei: namely the dentate nuclei, which are prominent in the diffusion-weighted image (F). The involvement of other cerebellar nuclei, such as fastigial, globosus, and emboliform nuclei, is not apparent. On DOI 135 (G–I), cerebellar atrophy is evident.

Using acute specimens, including throat swab, cerebrospinal fluid, and stool, we performed PCR-based screening for pathogenic viruses, such as herpes simplex virus 1 and 2, cytomegalovirus, varicella-zoster virus, parvovirus B19, human herpesvirus 6–8, Epstein-Barr virus, parechovirus, mumps virus, Japanese encephalitis virus, enterovirus, respiratory syncytial virus, and parainfluenza virus. Subsequently, human rhinovirus A was detected in his throat swab and cerebrospinal fluid [5]. We also examined (DOI 2) cerebrospinal fluid cytokines, such as interleukin-6, −4, −2, and −10; interferon-γ; and tumor necrosis factor-α [6]. All results were normal, except extremely elevated interleukin-6 levels (>5,000 pg/ml [reference levels, <6.2 pg/ml]).

After 5 months from the onset, his family moved to another prefecture; subsequently, his follow-up at our hospital was terminated.

3. Discussion

Human rhinovirus, in addition to enterovirus, belongs to the picornavirus family, which causes a diverse group of diseases [5]. Enterovirus is one of the most common pathogens in CNS viral infections, such as aseptic meningitis and encephalitis: enterovirus was detected in 93 (44%) out of 210 definitive CNS viral infections [7]. However, rhinoviral CNS infection is extremely uncommon, and only two cases have been reported to date [3,4]. Rhinovirus, species not-noted and B, were detected in the cerebrospinal fluid of a 5-month-old girl with *Haemophilus influenzae* meningitis, who recovered uneventfully, and a girl younger than 3 months with sepsis-like illness, for which no further details were provided, respectively. As a respiratory tract pathogen, rhinovirus has been well-investigated; in 308 children with or without asthma, coinfection of rhinovirus and pathogenic bacteria was associated with increased respiratory symptoms and asthma exacerbations [8]. As mentioned, one of the two previously reported CNS rhinovirus-positive cases was complicated with *H. influenzae* meningitis; moreover, rapid antigen detection test for group A streptococcus, using throat swab, was positive in our patient. Although this is still a mere speculation, bacterial coinfection might promote rhinoviral CNS penetration.

Rotavirus is the most common cerebellitis-causing organism and has been quite well-reported. Among 157 reported cases of acute cerebellitis, the causative organism was detected in 70 patients: rotavirus (20 patients), Epstein-Barr virus (5), varicella zoster (4), herpes simplex virus (2), respiratory syncytial virus (2), enterovirus (1), and so on [9]. In these reports on rotavirus- associated cerebellitis, the marked hyperintensity in DWI in the bilateral dentate nuclei (3 patients out of 3) and cerebrospinal fluid pleocytosis (cell count >10/μl, 9 patients out of 11) was common [10,11]. The cerebellitis typically develops soon after the onset of rotavirus gastroenteritis (an average of 2 days after onset of diarrheal illness); therefore, direct rotaviral invasion of the CNS has been speculated [9]. However, this has not been proven in all cases; Kobayashi et al. detected rotaviral nucleic acid in the CNS of 1 patient out of 2 [12]. Moreover, reports of cerebrospinal fluid cytokines are sparse; nonetheless, we have previously reported two cases of rotavirus-associated acute encephalitis/encephalopathy and concurrent cerebellitis [13]. Levels of all measured cerebrospinal fluid cytokines were normal in both patients, except extremely elevated interleukin-6 level in case 1 (9,092 pg/ml on DOI 3), while the concentration was 7.1 pg/ml in case 2 on DOI 31.

Did group A streptococcus play a role other than facilitating rhinoviral CNS penetration in our patient? Bacterial meningitis, as an invasive group A streptococcal infection, is unlikely because bacterial cultures of his blood and cerebrospinal fluid tested negative. Another possible explanation is immune-mediated cerebellitis, usually with a latency period between the prodromal and cerebellar symptoms, averaging 8.7 days (with a maximum of 60 days) [9]. Uchizono et al. reported the case of a 7-year- old girl with probable post-infection immune-mediated acute cerebellitis following the 7 days' latency period after group A streptococcal infection [14]. In the present case, we did not examine autoantibodies. However, our patient did not exhibit a prodromal or latency period; hence, we speculate that the possibility of immune-mediated cerebellitis is less plausible.

This could be the first report of rhinovirus-associated acute cerebellitis; however, the clinical course of our patient, including cerebrospinal fluid cytokine levels and MRI findings, corresponded well with previous reports on rotavirus-associated acute cerebellitis. There seem to be no specific symptoms or signs for suspecting rhinoviral CNS infection; therefore, further screening, using PCR to detect various viral pathogens, including rhinovirus, in presumably CNS-infected patients with or without accompanying bacterial infection, could be beneficial for delineating the various underlying CNS pathophysiologies.

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