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Case Report

Acute Disseminated Encephalomyelitis Associated With Influenza A H1N1 Infection

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ABSTRACT

Acute disseminated encephalomyelitis is an immune-mediated inflammatory disorder of the central nervous system, characterized by demyelination. Acute disseminated encephalomyelitis predominantly involves the white matter of the brain and spinal cord, and often follows upper respiratory tract infection. We describe a case of acute disseminated encephalomyelitis associated with the influenza A (H1N1) virus. The H1N1 virus usually causes febrile respiratory signs, e.g., fever, cough, and sore throat. Although these signs exhibit a self-limited course, the frequencies of severe complications and death are increasing. To date, only a few reports of acute disseminated encephalomyelitis secondary to the H1N1 virus have been published.

Introduction

Acute disseminated encephalomyelitis is an uncommon inflammatory demyelinating disease that usually presents in children and young adults. Acute disseminated encephalomyelitis usually follows an infection of the upper respiratory tract. Numerous pathogens have been associated with acute disseminated encephalomyelitis. For instance, viruses that have been implicated in this disorder include measles, rubella, varicella, influenza, Epstein-Barr virus, Coxsackie virus, coronavirus, human immunodeficiency virus, herpes simplex, cytomegalovirus, and West Nile virus. Other organisms associated with acute disseminated encephalomyelitis include hemolytic streptococcus (group A), *Mycoplasma pneumonia*, and leptospirosis [1,2]. Previous studies established that the influenza virus also represents a common causative agent of acute disseminated encephalomyelitis. However, only a few cases of acute disseminated encephalomyelitis secondary to influenza A (H1N1) virus have been reported in the literature [3-7].

Case Report

A 7-year-old boy was admitted with rapid onset of confusion and widespread neurologic deficits. At that time, he presented with fever, rhinorrhea, sore throat, and cough that began 5 days before admission. The boy was previously healthy, and he reported no history of any recent exposure to other medications, toxic substances, or previous vaccinations. Furthermore, the medical history of his family was unremarkable. The physical examination of the boy revealed mild tachycardia and pharyngeal hyperemia. A subsequent neurologic examination indicated the presence of confusion, lethargy, quadriplegia, and a bilateral extensor plantar response. Although a laboratory evaluation revealed a low leukocyte count (1910/mm^3), his serum C-reactive protein level and erythrocyte sedimentation rate were normal. Cranial computed tomography was performed, and the findings were unremarkable. Likewise, an examination of the patient's cerebrospinal fluid produced normal results, except for mild lymphocytic pleocytosis (100 cells/mm^3, all mononuclear, with normal protein and glucose), and the findings of an electroencephalogram were also unremarkable. Acyclovir and ceftriaxone were administered to the boy empirically. Cranial magnetic resonance imaging and magnetic resonance spectroscopy were then performed with a 1.5 T system (Siemens Magnetron Symphony, Erlangen, Germany). Magnetic resonance imaging indicated T_2 and fluid attenuated inversion recovery hyperintensity in the globus pallidus and

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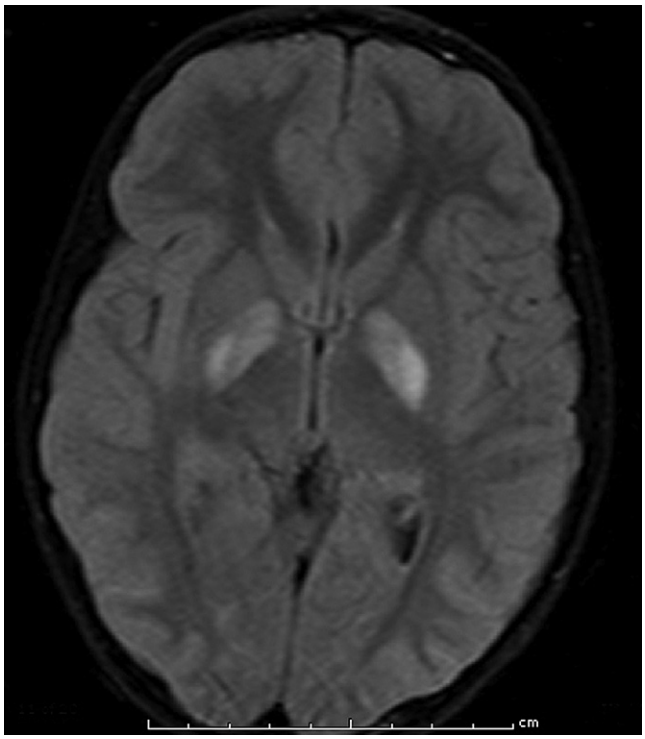

Figure 1. An axial magnetic resonance imaging section demonstrates lesions of the globus pallidus bilaterally. The lesions are hyperintense on T_2-weighted and fluid attenuated inversion recovery sequences.

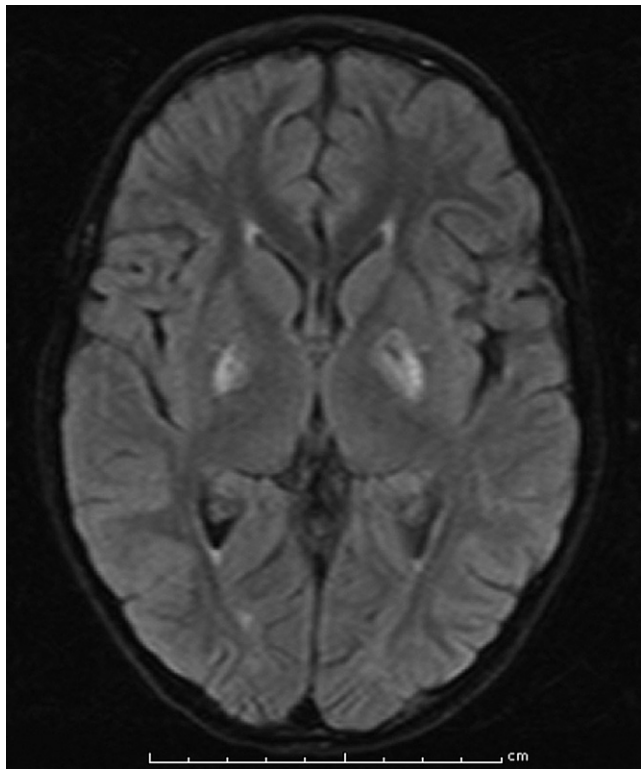

Figure 2. After 1 month, follow-up magnetic resonance imaging indicates a regression of the lesions.

cerebellar dentate nucleus and periaqueductal white matter bilaterally. After an intravenous injection of gadolinium, minimal enhancement was detected. In diffusion weighted images, no loss of diffusion was evident. However, magnetic resonance spectroscopy revealed no lactate peak corresponding to these lesions (Fig 1). Serum and cerebrospinal fluid lactate levels were normal, and his oligoclonal bands also tested negative.

Intravenous methylprednisolone (20 mg/kg/day) was administered for 3 days, with a presumed diagnosis of acute disseminated encephalomyelitis. After methylprednisolone, prednisone (1 mg/kg/day) was administered, and the drug was gradually withdrawn after 1 month. Serum markers for viruses (i.e., herpes simplex virus, cytomegalovirus, *Varicella zoster*, mumps, rubella, measles, and Epstein-Barr virus) as well as *Mycoplasma pneumonia* produced negative results. However, influenza A (swine origin H1N1 serotype) was detected in a nasopharyngeal swab specimen by enzyme immunoassay on day 6, and oseltamivir was administered to the boy. Because of the persistence of neurologic signs, intravenous immunoglobulin (1 g/kg/day) was initiated on day 23 after admission, and was administered for 2 days. During a follow-up examination at the end of treatment, magnetic resonance imaging was performed, and revealed a significant regression of the lesions (Fig 2). The boy was subsequently discharged with anarthria and quadriparesis on day 34 after admission. A follow-up appointment revealed that the boy continued to manifest anarthria and quadriparesis 2 years after the initial attack.

Discussion

Neurologic complications were previously described in association with respiratory tract infections with seasonal influenza A or B viruses, including seizures, encephalitis, encephalopathy, Reye syndrome, and other neurologic disorders. Influenza A viruses represent a continuous pandemic threat. In April 2009, a novel influenza A virus, the so-called swine-origin influenza A (H1N1) virus, was isolated. Although unfavorable outcomes were mostly related to pulmonary complications, neurologic complications can occur after respiratory tract infections with the novel influenza A (H1N1) virus [8]. The literature has established that the influenza virus is a common causative agent of acute disseminated encephalomyelitis. However, only a few case reports of acute disseminated encephalomyelitis secondary to influenza A (H1N1) virus have been presented in the literature [3-7]. Here, we describe a child with acute disseminated encephalomyelitis associated with influenza A (H1N1) virus. To the best of our knowledge, this report represents only the fifth case of acute disseminated encephalomyelitis secondary to influenza A (H1N1) virus in children.

The typical neuroradiologic findings of acute disseminated encephalomyelitis include multiple inflammatory lesions in the brain and spinal cord, particularly in the white matter. Usually these lesions are evident in the subcortical and central white matter and in the cortical gray-white matter junction of both cerebral hemispheres, the cerebellum, the brainstem, and the spinal cord. In addition, studies suggest that the periventricular white matter and gray matter of the cortex, thalami, and basal ganglia may also be involved [9]. Here, we report that acute disseminated encephalomyelitis is associated with an infection of influenza A (H1N1).

Acute disseminated encephalomyelitis should be differentiated from acute necrotizing encephalopathy. Acute necrotizing encephalopathy after a febrile illness is characterized by a rapid deterioration of consciousness, an elevation of serum aminotransferases, and multifocal, symmetric lesions evident on computed tomography or

magnetic resonance imaging in the thalamus, cerebral and cerebellar medullae, and brainstem. The presence of hemorrhage and localized tissue loss on magnetic resonance images in the thalami and brainstem suggest acute encephalopathy [10]. Our patient's liver enzymes were normal, and no hemorrhage or atrophy was detected on magnetic resonance imaging.

Mitochondrial disorders are also included in the differential diagnosis of disorders associated with acute central and peripheral demyelination. The typical neuroradiologic findings of mitochondrial disease include abnormal magnetic resonance imaging results in the T_2-weighted signal of the cerebral white matter, cerebellar atrophy, and abnormalities of deep gray matter nuclei. Elevated lactate levels on proton magnetic resonance spectroscopy were also proposed as useful diagnostic criteria for indicating mitochondrial disease [11,12]. Although clinical evidence is still lacking, a mitochondrial disorder should be considered when bilateral symmetric lesions of the basal ganglia are present [11,12]. For the patient in this study, mitochondrial disorders were excluded because his serum and cerebrospinal fluid lactate levels were normal, and H-proton magnetic resonance spectroscopy revealed no lactate peak.

The widely accepted first-line treatment for acute disseminated encephalomyelitis involves high doses of intravenous corticosteroids such as methylprednisolone. This treatment is followed by 3-6 weeks of gradually decreasing oral doses of prednisolone. Plasmapheresis, intravenous immunoglobulin, mitoxantrone, and cyclophosphamide also comprise alternative methods of therapy [13]. In our patient, we first administered intravenous methylprednisolone (20 mg/kg/day) for 3 days. After we obtained positive serologic results for influenza A (H1N1) virus, we began treatment with oseltamivir. Because of the persistence of neurologic signs, intravenous immunoglobulin (1 g/kg/day) was also administered for 2 days.

Acute disseminated encephalomyelitis is usually a self-remitting disease. Approximately 70% of patients demonstrate complete recovery. However, permanent neurologic deficits remain in 10-20% of patients [14]. The outcomes of patients presenting with influenza A (H1N1) virus-associated acute disseminated encephalomyelitis usually involve complete recovery or minor sequelae. To the best of our knowledge, Rellosa et al. in 2011 were the first to describe a 5-year-old boy with acute disseminated encephalomyelitis associated with influenza A (H1N1) virus [3]. However, their patient presented with partial status epilepticus, and received a full course of oseltamivir and antiepileptic treatment without intravenous immunoglobulin or methylprednisolone. After his treatment, the patient demonstrated a favorable outcome. Wang et al. reported on the usefulness of therapy for acute disseminated encephalomyelitis with a combination of intravenous immunoglobulin, methylprednisolone, and oseltamivir in an adult patient [4]. In addition, Yıldıztaş et al. reported on a neurologic complication of H1N1 influenza virus in children [5]. They described a 6-year-old boy with acute disseminated encephalomyelitis who fully recovered after intravenous immunoglobulin and oseltamivir, without methylprednisolone treatment. On the other hand, our patient recovered with severe neurologic sequelae after combined treatment with intravenous immunoglobulin, methylprednisolone, and oseltamivir.

Conclusion

Because of the rarity of similar case reports in the literature, this child represents an interesting case of acute disseminated encephalomyelitis associated with the influenza A (H1N1) virus. The manifestations observed in our patient suggest that outcomes in acute disseminated encephalomyelitis associated with the influenza A (H1N1) virus may not always be benign, despite an apparent resolution of magnetic resonance imaging abnormalities. The early recognition of H1N1 is important because rapid treatment for the H1N1 virus could exert some positive effects that did not occur in this case. We hope to draw the attention of clinicians to the benefits of antiviral treatment, initiated as soon as possible after the onset of illness.

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