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Case Report Mild Encephalopathy With Splenial Lesion and Parainfluenza Virus Infection

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ARTICLE INFORMATION	ABSTRACT
Article history: Received 27 August 2012 Accepted 19 November 2012	Mild encephalopathy with reversible splenial lesions has mainly been associated with influenza A and B virus infection. Patients present with neurologic symptoms 1 to 3 days after a prodromal illness and recover completely within a few days. Magnetic resonance imaging typically shows reversible lesions with reduced diffusion in the corpus callosum, predominantly in the splenium. We report on a 5-year old Caucasian boy who was referred with recurrent seizures and decreased level of consciousness after a 2-day prodromal fever and cough. Magnetic resonance imaging showed cytotoxic edema of the entire corpus callosum and the adjacent periventricular white matter with diffusion restriction and faint T ₂ -hyperintensity. Parainfluenza virus type 1-3 infection was documented by direct immunofluorescence in the initial nasopharyngeal swab, but polymerase chain reaction for parainfluenza virus type 1-4 in the cerebrospinal fluid remained negative. This is—to our knowledge—the first description of mild encephalopathy with reversible splenial lesions in association with parainfluenza virus infection. The pathogenesis of mild encephalopathy with reversible splenial lesions, however, still remains unclear, and further studies investigating detailed mechanisms that lead to the typical brain lesions are warranted.

Introduction

Mild encephalopathy with reversible splenial lesions (MERS) in children has been mainly associated with influenza virus A and B [1-5]. Affected patients present with neurologic symptoms 1 to 3 days after a prodromal illness consisting of fever, cough, and rhinorrhea. The most common symptom is delirious behavior (54%), followed by decreased level of consciousness (35%) and seizures (33%) [3]. Patients recover completely within a few days. Characteristic magnetic resonance imaging (MRI) findings include reversible lesions with transiently reduced diffusion in the corpus callosum, at least involving the splenium of the corpus callosum, and are sometimes associated with symmetrical white matter lesions [3]. MERS has mainly been

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described in patients of South-East-Asian origin, and only few reports from Europe [1] or North America [2] have been published. Besides pathognomonic MRI findings, hyponatremia and cerebrospinal fluid pleocytosis are observed in some patients with MERS. Electroencephalography abnormalities are found in approximately half of patients, including diffuse slow waves, occipital slow waves, and focal spikes [3]. Similar MRI findings, as found in patients with MERS because of influenza virus A and B, have been described in association with other infectious diseases such as mumps virus, adenovirus, rotavirus, streptococci, *Escherichia coli*, and *Salmonella enteritidis* [3]. We here report a 5-year-old patient who had MERS in the context of a human parainfluenza virus infection.

Case Report

A 5-year-old Caucasian boy was referred to our emergency department with recurrent seizures and decreased level of consciousness after a 2-day prodromal illness with fever and cough. There was no family





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history of neurologic disorders. He presented with a Glasgow Coma Scale of 9 and showed slight nuchal rigidity. On clinical examination there were no focal neurologic signs but signs of upper respiratory tract infection. Laboratory investigations revealed an elevated C-reactive protein level (110 mg/L) with normal blood cell count. Biochemical examination results including serum electrolytes (notably serum sodium level) remained without abnormalities. Cerebrospinal fluid examinations showed pleocytosis (83 \times 10E6/l) with a predominance of polymorphonuclear cells (65 \times 10E6/l), normal glucose level (3.29 mmol/L) with a normal glucose ratio (liquor/plasma) of 0.63, and a normal protein level (0.54 g/L). Electroencephalography showed slowed background activity, but no seizure-related activity was noted. In a respiratory sample taken with a nasopharyngeal swab, direct immunofluorescence (D3 Ultra DFA Respiratory Virus Screening & ID Kit [Diagnostic Hybrids]) for parainfluenza virus 1-3 was reactive. Other respiratory viruses were not detectable. Microbiologic testing for herpes simplex virus, tick-borne encephalitis virus, Epstein-Barr virus, varicella-zoster virus, cytomegalovirus, measles, mumps, rubella, Borrelia burgdorferi, and Mycoplasma pneumoniae remained negative. On MRI the entire corpus callosum and the adjacent periventricular white matter showed a hyperintensity on b1000 diffusion-weighted images with reduced apparent diffusion coefficient reflecting restricted diffusion. The diffusion abnormalities were accompanied by faint T₂ hyperintensity in the affected structures (Fig 1A,B). The patient was treated empirically with ceftriaxone and aciclovir until the result of bacteriologic cultures and polymerase chain reaction for herpes simplex virus in the cerebrospinal fluid proved to be negative. We were not able to detect parainfluenza virus 1-4 in the cerebrospinal fluid by polymerase chain reaction (Luminex xTAG Respiratory Viral Panel Fast; Luminex Molecular Diagnostics; Toronto, Ontario, Canada). The patient gradually became alert and had completely recovered without sequelae within 1 week. He was seen for a follow-up examination 2 months after the acute episode. The course has been uneventful, and the clinical examination did not show any neurologic abnormalities.

Discussion

We describe a 5-year-old Caucasian boy presenting with recurrent seizures and decreased level of consciousness showing MRI lesions with restricted diffusion in the corpus callosum and symmetrical white matter lesions—such as previously reported in MERS. The condition was associated with an infection by human parainfluenza virus.

Human parainfluenza viruses are important pathogens for respiratory tract infections in children and adults. Symptoms are variable and range from coldlike symptoms to acute infectious croup and severe pneumonia. Nonrespiratory symptoms involve Guillan-Barré syndrome, myocarditis, and meningitis [6-8]. Reports on MRI abnormalities in children with human parainfluenza virus infections are scarce and describe brain lesions compatible with acute necrotizing encephalopathy [8]. The association of MERS and para-influenza virus infection has not been described previously.

MERS describes a symptom complex including reversible neurologic symptoms associated with characteristic MRI findings (reduced diffusion in the corpus callosum and white matter lesions) [3]. The largest series described 54 patients. A large variety of infectious pathogens were detected—mainly influenza A and B. In 41% of patients, the causative pathogen remained unknown [3]. Similar findings have been described in noninfectious conditions, such as antiepileptic medication [9] and Kawasaki disease [10].

The pathogenesis of MERS remains unknown so far. Several mechanisms have been proposed. Foremost, reduced diffusion in the splenium, as documented by MRI, has been explained by transient development of intramyelinic or interstitial edema [3]. Hyponatriemia, which is frequently seen in conjunction with MERS [11], could potentiate such an edema. Alternatively, local infiltration by inflammatory cells could lead to reduced diffusion on MRI. Similar to our patient, 13 of 43 patients with MERS presented pleocytosis as a sign of inflammation in the central nervous system [3]. This is corroborated by one report that documented elevated cytokine levels in the cerebrospinal fluid of a patient with MERS [12]. On the other hand, the cerebrospinal fluid cytokine profiles reported in several patients with MERS indicate that axonal damage is not involved [13]. Furthermore, autoimmune reactions have been related to MERS. A Japanese group described a patient with mild encephalopathy with reversible splenial lesions and anti-glutamate E₂ receptor antibodies in the cerebrospinal fluid [14]. Although several pathogenic mechanisms have been proposed for MERS, no explanation for the tissue tropism of the lesions has been found.

Finally, unidentified genetic factors are likely involved in the pathogenesis of MERS. First, the condition has repeatedly been observed in patients from South-East Asia, but only rarely in non-Asiatic patients [1,2]. Second, familial cases have been reported [15].

Similar to other reports in the literature, we cannot prove a firm association of parainfluenza virus infection with MERS in our case, because we were not able to document parainfluenza virus in the cerebrospinal fluid. This might be due to the fact, that the Luminex xTAG Respiratory Viral Panel Fast

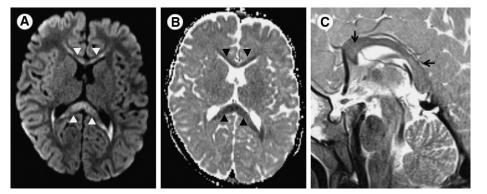


Figure 1. The corpus callosum shows bright signal (arrowheads) on the b1000 diffusion-weighted image (A), accompanied by reduced signal (arrowheads) on the corresponding apparent diffusion coefficient map (B) and faint hyperintensity (arrows) on the sagittal T₂-weighted image (C).

is not validated for examinations in cerebrospinal fluid. Nevertheless, parainfluenza virus was detected in the nasopharyngeal secretion by immunofluorescence, indicating active infection. Because of the close temporal association of parainfluenza virus infection and MERS, we suggest a causal relation. An extensive search for other causes remained negative, there was no evidence of hyponatriemia, and no similar cases in the family history were noted.

We propose that future studies regarding mild encephalopathy with reversible splenial lesions involve larger study groups and suggest that standardized neuroinflammatory investigations involving inflammatory markers, cytokines, and autoantibodies are performed in the serum and the cerebrospinal fluid. Genetic studies involving nextgeneration sequencing approaches might clarify the questions with regard to genetic disposition.

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