Brain & Development 37 (2015) 618–624

BRAIN & DEVELOPMENT
Official Journal of the Japanese Society of Child Neurology

www.elsevier.com/locate/braindev

Original article

Differential diagnosis of delirious behavior in children with influenza

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Received 22 February 2014; received in revised form 5 September 2014; accepted 10 September 2014

Abstract

Delirious behavior (DB) in children infected with influenza virus is an important symptom associated with encephalopathy. As children with influenza-associated DB with encephalopathy may require therapy whereas children with influenza-associated DB without encephalopathy do not, distinguishing between these conditions is essential. To clarify these differences and identify the most common features of acute encephalopathy, we retrospectively reviewed the clinical course, laboratory data, magnetic resonance imaging (MRI) and electroencephalography (EEG) findings, therapy, and prognosis of 48 children with influenza exhibiting DB. Of the 48 children, 37 and 11 were diagnosed with influenza A and B, respectively. Moreover, 40 were diagnosed with DB without encephalopathy (DBNE group) and 8, with DB with encephalopathy (DBE group). Reversible splenial lesion (RESLE) was detected in 7 patients in the DBNE group, mild encephalitis/encephalopathy with a reversible splenial lesion (MERS) in 2 patients, and a mild form of acute encephalopathy with biphasic seizures and late reduced diffusion in 1 patient in the DBE group. Serum sodium levels <136 mEq/L were observed in 28 cases. Disturbance of consciousness was observed in 25 cases, seizure in 20, and slow waves on EEG in 22. Methylprednisolone pulse therapy was administered in 8 cases. No cases of neurological sequelae were observed. Although most of the clinico-radiological features of the DBNE and DBE groups did not differ substantially, marked differences were observed in the age at onset, initial neurological symptoms, duration of DB, rate of seizure, and slowing of background activity on EEG. These differences should be considered when distinguishing between DBNE and DBE in children.

Keywords: Delirious behavior; Encephalopathy; Differential diagnosis; Disturbance of consciousness; Seizure; Age; Influenza; Reversible splenial lesion during febrile illness

1. Introduction

Among the various medical conditions that can cause delirious behavior (DB) in children, infection is the most common cause [1]. Moreover, among the types of infections and conditions associated with DB, influenza-associated encephalopathy is a very common cause [2]. Thus, DB is regarded as an important, early-stage symptom of influenza-associated encephalopathy [3]. DB is a particularly prevalent symptom in children with this condition, including Japan. In 2001, the Annual Report of the National Research Committee on influenza-associated encephalopathy reported that DB was

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http://dx.doi.org/10.1016/j.braindev.2014.09.003
0387-7604/

observed during the early period of the disease in 30 of 70 Japanese children who died from influenza-associated encephalitis/encephalopathy. In accordance with this finding, more than 10% (299 of 2846) of Japanese children diagnosed with influenza in 2006 exhibited DB during the course of illness [4]. Moreover, during the novel pandemic influenza A infection of 2009, 53% (99 of 188) of Japanese children diagnosed with virus-associated encephalopathy exhibited DB [5].

Meanwhile, DB is also often observed in children with influenza but without encephalopathy [6–8]. Based on our previous identification of a relationship between DB and reversible splenial lesion during febrile illness (RESLEF), a condition that encompasses a wide spectrum of clinico-radiological features ranging from only DB to encephalopathy with neurological sequelae, we proposed the use of the term "RESLEF spectrum syndrome" to refer to RESLEF characterized by DB [9]. In cases of children with DB, differential diagnosis should be performed with the knowledge that they present with a spectrum of clinico-radiological features. Furthermore, it is important to distinguish between these conditions, because children with influenza-associated DB with encephalopathy may require therapy whereas children with influenza-associated DB without encephalopathy do not [10].

Despite our previous research, the differences between the clinico-radiological features of influenza-associated DB in children with and without encephalopathy remain unclear. To clarify these differences, we retrospectively analyzed several of the most commonly studied characteristics including clinical course, laboratory data, magnetic resonance imaging (MRI) and electroencephalography (EEG) findings, therapy administered, and prognosis in groups of children with influenza-associated DB with and without encephalopathy. We subsequently compared the results to identify the features most commonly associated with each condition to assist in their more precise differentiation in children.

2. Subjects and methods

The subjects were selected from among all children admitted for the treatment of influenza infection at a single hospital between January 2009 and March 2013. Influenza was diagnosed on the basis of a rapid antigen-detection assay using a nasopharyngeal swab. Of the 368 children who had been hospitalized for influenza, 77 were diagnosed with influenza-associated DB. This retrospective study included influenza-associated DB patients who underwent both MRI and EEG within 96 h of DB onset. We excluded influenza-associated DB patients who did not undergo either or both MRI and EEG within 96 h of DB onset. Of these 77 patients, 48 met all study criteria.

MRI and EEG were performed within 96 h (35.2 ± 24.5 h for MRI and 26.0 ± 19.4 h for EEG) of DB onset. MRI follow-up was conducted in all cases except one owing to patient unavailability to undergo MRI to confirm normalization of splenial and subcortical white matter (SCWM) lesions. EEG follow-up was performed in all cases in which the initial recording showed any abnormality, except one case owing to patient unavailability.

We defined disturbance of consciousness (DC) as a score $\geqslant 10$ in the Japan Coma Scale or $\leqslant 13$ in the Glasgow Coma Scale [3]; these scales are coma scales for evaluating arousal in consciousness by reaction to stimulation. Consciousness has 2 major components: arousal and content [11,12]. Therefore, to precisely evaluate consciousness, it must be assessed on the basis of arousal and content. It is impossible to assess the content of consciousness in patients with severe impairment in arousal of consciousness. Furthermore, content requires arousal, but arousal can be present without content. In this study, DC was defined as a disturbance in the arousal of consciousness, while DB was defined as a disturbance in content of consciousness. In children in particular, it is difficult to correctly assess content of consciousness owing to immature verbal function. Therefore, DC in children is generally evaluated by arousal of consciousness in clinical practice. Consequently, DB is sometimes intermittently observed after children are evaluated by reaction to stimulation with full arousal level.

We carefully obtained the patients' medical history and evaluated consciousness during hospitalization from fever onset. When distinguishing sleep and DC was difficult by reaction to stimulation, they were distinguished using EEG according to arousal response, alpha waves during wakefulness, spindle waves during sleep, and high-voltage slow waves on EEG. DB was defined as clinical features including visual hallucinations, non-visual sensory misperceptions (e.g., auditory hallucinations), unexpected emotional changes (e.g., inappropriate laughter and fear), incoherent speech, purposeless movement, and impulsive behavior [7,8]. Patients exhibited DC continually for a certain period while they often exhibited DB intermittently. DB typically continued intermittently during the clinical course of DC, whereas we sometimes judged that DB had continued intermittently clinically after the patient had achieved clear consciousness.

Therefore, the patients were divided into 2 groups: the DB without encephalopathy (DBNE) group, which consisted of patients who exhibited DB only once or intermittently, during which DC clinically lasted for less than 12 h throughout the clinical course; and the DB with encephalopathy (DBE) group, which consisted of patients who experienced DB once or intermittently, during which DC lasted for more than 12 h throughout