Brain & Development 37 (2015) 463–470

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

www.elsevier.com/locate/braindev

Original article

Clinical and genetic features of acute encephalopathy in children taking theophylline

Makiko Saitoh [a,*], Mayu Shinohara [a], Atsushi Ishii [b], Yukiko Ihara [b], Shinichi Hirose [b], Masashi Shiomi [c], Hisashi Kawawaki [d], Masaya Kubota [e], Takanori Yamagata [f], Akie Miyamoto [g], Gaku Yamanaka [h], Kaoru Amemiya [i], Kenjiro Kikuchi [j], Atsushi Kamei [k], Manami Akasaka [k], Yuki Anzai [l], Masashi Mizuguchi [a]

[a] *Department of Developmental Medical Sciences, Graduate School of Medicine, The University of Tokyo, Japan*
[b] *Department of Pediatrics, Fukuoka University, Japan*
[c] *Department of Pediatrics, Child Medical Center, Osaka City General Hospital, Japan*
[d] *Department of Pediatric Neurology, Child Medical Center, Osaka City General Hospital, Japan*
[e] *Department of Neurology, National Center for Child Health and Development, Japan*
[f] *Department of Pediatrics, Jichi Medical University, Japan*
[g] *Department of Pediatrics, Asahikawa Habilitation Center for Disabled Children, Japan*
[h] *Department of Pediatrics, Tokyo Medical University, Japan*
[i] *Department of Neurology, Tokyo Metropolitan Hachioji Children's Hospital, Japan*
[j] *Division of Neurology, Saitama Children's Medical Center, Japan*
[k] *Department of Pediatrics, Iwate Medical University, Japan*
[l] *Department of Pediatrics, Saiseikai Yokohamashi Tobu Hospital, Japan*

Received 21 May 2014; received in revised form 30 July 2014; accepted 30 July 2014

Abstract

Background: Theophylline has recently been suspected as a risk factor of acute encephalopathy with biphasic seizures and late reduced diffusion (AESD), although there has been no systematic study on the relationship between acute encephalopathy in children taking theophylline (AET) and AESD.

Methods: We recruited 16 Japanese patients (11 male and 5 female, median age of 2 years and 7 months) with AET from 2008 to 2013. We evaluated their clinical features, such as the duration of first seizure, biphasic clinical course and cranial CT/MRI imaging and compared them with those of AESD. We analyzed the polymorphisms or mutations of genes which are associated with AESD.

Results: Clinically, 12 patients had neurological and/or radiological features of AESD. Only one patient died, whereas all 15 surviving patients were left with motor and/or intellectual deficits. Genetically, 14 patients had at least one of the following polymorphisms or mutations associated with AESD: thermolabile variation of the carnitine palmitoyltransferase 2 (*CPT2*) gene, polymorphism causing high expression of the adenosine receptor A2A (*ADORA2A*) gene, and heterozygous missense mutation of the voltage gated sodium channel 1A (*SCN1A*) and 2A (*SCN2A*) gene.

* Corresponding author. Address: Department of Developmental Medical Sciences, Graduate School of Medicine, The University of Tokyo, 7-3-1 Hongo, Bunkyo, Tokyo 113-0033, Japan. Tel.: +81 3 5841 3615; fax: +81 3 5841 3628.
E-mail address: makisaito-tky@umin.ac.jp (M. Saitoh).

http://dx.doi.org/10.1016/j.braindev.2014.07.010

Conclusions: Our results demonstrate that AET overlaps with AESD, and that AET is a multifactorial disorder sharing a genetic background with AESD.

Keywords: Theophylline; Adenosine receptors; Acute encephalopathy; Status epilepticus

1. Introduction

Theophylline is a methylxanthine that exerts multiple pharmacologic effects by inhibiting phosphodiesterases. Until recently, it has been commonly used in clinical practice for the treatment of bronchial asthma and acute bronchitis, especially in Japan. However, theophylline may trigger seizures in patients with or without epilepsy, even when the concentration is within the therapeutic range [1,2]. The pro-convulsive effects of theophylline are explained by its activity as a non-selective, competitive antagonist of adenosine. In the central nervous system (CNS), adenosine plays a role as an endogenous anticonvulsant [3,4], since the effects of anti-excitatory A1 receptor (ADORA1) predominate over those of pro-excitatory A2A receptor (ADORA2A). Theophylline-associated seizures (TASs) are most prevalent among children under 6 years of age and usually occur during a febrile infectious disease [5]. TASs often persist and resist first-line anticonvulsants, leading to refractory status epilepticus and a poor neurologic outcome [6,7].

When a post-ictal coma lasts for more than 24 h, the condition should be regarded as acute encephalopathy rather than a mere seizure [8]. Acute encephalopathy with inflammation-mediated status epilepticus includes multiple syndromes [9], such as fever-induced refractory epileptic encephalopathy in school-aged children (FIRES) (or its eponym, acute encephalitis with refractory, repetitive partial seizures (AERRPS)), and acute encephalopathy with biphasic seizures and late reduced diffusion (AESD) [10] (or its eponym, acute encephalopathy with febrile convulsive status epilepticus (AEFCSE)) [11]. In a case series in a referral hospital in Japan, many children taking theophylline reportedly had clinical and radiological features of AESD or AEFCSE [12]. Thus, theophylline has recently been suspected as a risk factor of AESD [8], although there has been no systematic study on the relationship between acute encephalopathy in children taking theophylline (AET) and AESD.

In this paper, we recruited Japanese patients with AET by means of a nationwide, multi-institutional study supported by the Japanese Society of Child Neurology. We reviewed their clinical data and examined whether the findings meet the diagnostic criteria of AESD. We also conducted genetic analysis of these patients, focusing on genes that were shown to be associated with AESD in our previous studies: carnitine palmitoyltransferase 2 (*CPT2*), *ADORA2A*, and voltage-gated sodium channel subunit 1A (*SCN1A*) and 2A (*SCN2A*) [12–15]. The aim of this study was to elucidate the relationship between AET and AESD from both clinical and genetic viewpoints.

2. Methods

2.1. Patients

We defined acute encephalopathy based on the following criteria [16,17]: (1) acute onset of severe and sustained impairment of consciousness after a preceding infection, and (2) exclusion of CNS inflammation. We defined AET as acute encephalopathy with the onset with status epilepticus within several hours after administration of oral theophylline or intravenous aminophylline, and recruited patients with AET from hospitals in Japan during 2008–2012 in a retrospective manner. Sixteen Japanese patients (11 male and 5 female) aged from 6 months to 4 years and 4 months (median, 2 years and 7 months), participated in this study. One case (Case 2) had been reported previously [14]. Their clinical characteristics including the family and past history, preceding infection, serum concentration of theophylline, duration of status epilepticus, presence or absence of biphasic seizures, cranial CT and/or MRI findings, therapy and outcome, were evaluated. The diagnosis of AESD was based on the criteria described previously [16]. It was regarded as 'definite' when both the characteristic clinical course (biphasic seizures) and CT/MRI findings (delayed appearance of cerebral cortical edema, distribution of lesions showing lobar or hemispheric involvement and peri-Rolandic sparing, and restricted diffusion of the subcortical white matter (so-called bright tree appearance) were present [8,10], 'probable' when either clinical or CT/MRI features were present, and 'possible' when prolonged febrile seizures were followed by non-specific CT/MRI findings (diffuse cortical damage) and other diagnostic possibilities were unlikely. In some patients whose CT/MRI findings in the acute/subacute period were either unavailable or insufficient, distribution of lesions was inferred on the basis of those in the convalescence. Other conditions that occasionally show bright tree appearance, such as hemorrhagic shock and encephalopathy syndrome, head