Clinical Profile and Changes of Serum Lipid Levels in Epileptic Patients after Cerebral Infarction

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Background: Antiepileptic drugs (AEDs) may increase development of dyslipidemia and cerebrovascular disease (CVD). We examined the clinical profile and changes of serum lipid levels after AED monotherapy in patients with poststroke epilepsy (PSE) after cerebral infarction (CI). *Subjects and methods:* Medical records were reviewed in consecutive 2144 CI patients. Monotherapy of valproate, carbamazepine (CBZ), phenytoin (PHT), zonisamide, levetiracetam, or lamotrigine was performed in PSE patients. Serum lipid levels were measured before and at 3 months after AED treatment. *Results:* The prevalence of PSE was 7.0% in CI patients. The TOAST etiology disclosed large-artery atherosclerosis in 68 patients (45%), cardioembolism in 63 patients (42%), and undetermined cause in 19 patients (13%). CVD risk profile showed obesity of 18 patients (12%), current smoker of 30 patients (20%), hypertension of 75 patients (50%), diabetes mellitus of 32 patients (21%), dyslipidemia of 15 patients (10%), and atrial fibrillation of 63 patients (42%). CBZ or PHT administration increased serum total cholesterol (TC) and low-density lipoprotein-cholesterol (LDL-C) levels significantly compared to baseline and AED-untreated controls. Those levels were not increased significantly in other AED and control groups. Serum high-density lipoprotein-cholesterol and triglyceride levels did not differ statistically in all groups. *Conclusions:* The prevalence of post-CI epilepsy was 7.0%. The pathogenesis contributed to atherothrombosis and cardioembolism. CBZ or PHT administration increased serum TC and LDL-C significantly. Thus, we should pay more attention to serum lipid levels in patients receiving cytochrome P450 (CYP)-induced AEDs, and might considerer switching to non–CYP-induced AEDs in patients with unfavorable serum lipid changes.
Key Words: Postischemic stroke epilepsy—clinical profile—antiepileptic drug—cytochrome P450—serum lipid levels.

Introduction

Dyslipidemia is a well-known risk factor for developing cardiovascular and cerebrovascular disease (CVD).[1,2] Some antiepileptic drugs (AEDs) seem to have a higher risk for developing dyslipidemia.[3] Previous studies indicated that older AEDs of phenytoin (PHT), carbamazepine (CBZ), or phenobarbital could induce the hepatic cytochrome P450 (CYP) system, leading to an elevation of serum lipid levels.[4] Those AEDs also increased C-reactive protein and homocysteine levels.[5,6]

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Received September 20, 2016; revision received October 23, 2016; accepted November 13, 2016.

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1052-3057/$ - see front matter

http://dx.doi.org/10.1016/j.jstrokecerebrovasdis.2016.11.011

Stroke is a common cause of epilepsy in elderly patients, and a prospective population-based study reported previously that stroke accounted to 45% of seizures onset after the age of 60.[7] The management of epilepsy after stroke events is a difficult issue occasionally. Current guidelines recommend that recurrent poststroke seizures can be treated with AEDs.[8,9] The optimal timing of initiation, the administration duration, and kinds of AEDs are controversial in patients with poststroke epilepsy (PSE).[10]

Compared to the general population, people with epilepsy had a 7-fold increased risk of CVD.[11,12] Exposure to CYP-induced AEDs may prompt atherosclerosis.[13,14] However, little is known how monotherapy of older and new AEDs influences serum lipid levels in patients with postischemic stroke epilepsy. Herein we aimed to examine the prevalence, clinical features, and changes of serum lipid levels after a single AED administration in Japanese patients with epilepsy that occurred first after cerebral infarction.

Subjects and Methods

Study Participants

Medical records were reviewed in consecutive 2144 patients (1240 men and 904 women) who were diagnosed with acute cerebral infarction and admitted to our department between January 2009 and December 2015.

Diagnosis and Classification of Postischemic Stroke Epilepsy

Acute symptomatic seizures and PSE were diagnosed according to the definition of the International League Against Epilepsy (ILAE).[15-17] Poststroke seizures were divided into 2 categories by the timing of onset: early-onset seizure (ES) within 7 days after cerebral infarction and late-onset seizures (LS) after 8 days poststroke. In the present study, postischemic stroke epilepsy was diagnosed within 6 months after acute cerebral infarction. The prevalence of PSE was determined in patients with cerebral infarction. Seizures were classified as generalized seizure or partial seizure, including simple, complex, and secondary generalized seizure.

The TOAST Etiology and CVD Risk Factors in Epileptic Patients after Cerebral Infarction

According to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification,[18] the etiology of cerebral infarction was determined in patients with postischemic stroke epilepsy. In those patients, CVD risk factors were analyzed on the following 6 items: obesity (body mass index $\geq 25.0\ kg/m^2$); current smoker; hypertension (systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥ 90 mm Hg) or currently under treatment; diabetes mellitus (fasting blood sugar ≥ 126 mg/dL or hemoglobin $A_{1c} \geq 6.5\%$) or currently under treatment; dyslipidemia (serum low-density lipoprotein-cholesterol [LDL-C] ≥ 140 mg/dL or high-density lipoprotein-cholesterol [HDL-C] < 40 mg/dL) or currently under treatment; and atrial fibrillation.

AED Administration

AED treatment included valproate (VA), CBZ, PHT, zonisamide (ZNS), levetiracetam (LEV), and lamotrigine (LTG). To evaluate changes of serum lipid levels after AED monotherapy, single administration of these AEDs was performed for ≥3 months. These AEDs were given according to clinical classification of epilepsy, the traditional treatment for PSE,[19] and the latest report of ILAE.[20] The final selection of single AED was determined by attending physicians. Patients with multiple AED medication (≥2 drugs) were excluded from the serological analyses of lipid changes.

Measurement of Serum Lipid Levels in PSE Patients and AED-Untreated Controls

Blood samples were obtained at 7-8 am before breakfast to avoid bias through diurnal variation. To examine whether the natural course or the hospital diet can influence serum lipid levels after cerebral infarction, control patients without AED medication were set from nonepileptic-admitted patients who was diagnosed serially as large-artery atherosclerosis, cardioembolism, or undetermined cause. Serum levels of total cholesterol (TC), LDL-C, HDL-C, and triglyceride (TG) were measured before and at 3 months after AED administration in epileptic patients, and at admission and the next 3 months in control patients. Statin users and patients with severe degree of liver dysfunction were excluded from the serological lipid study. The present study was carried out in strict accordance with the recommendation of the Guide for Clinical Studies of Toho University. The protocol was approved by the Committee on the Ethics of Human Research of Toho University Omori Medical Center.

Statistical Analysis

Statistical analyses used Student's *t*-test and one-way analysis of variance, followed by the Bonferroni multiple comparison for post hoc test of significant pairwise differences. All significance levels were set at .05.

Results

Prevalence and Etiology of PSE Patients after Cerebral Infarction

A total of 150 patients (83 men and 67 women) were diagnosed as epilepsy after cerebral infarction. The prevalence of postischemic stroke epilepsy was 7.0% (6.7% in men and 7.4% in women). The TOAST classification of these patients reveled large-artery atherosclerosis