Effects of valproate on the carotid artery intima-media thickness in epileptics

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ABSTRACT

Objective: The objective was to explore the effects of valproate (VPA) on the carotid artery intima-media thickness (CA-IMT) in epileptics.

Materials and Methods: A total of 30 epileptic patients treated with VPA was included as disease group, while 33 healthy people who matched general basic demographic details were the control group. The IMTs of the left and right carotids of the both groups were measured, and the average CA-IMT was calculated. The IMT-related risk factors were acquired for the univariate and multivariate analysis.

Results: The bilateral carotid and average CA-IMTs of the disease group were significantly higher than the control group (P < 0.001). The multivariate gradual regressive analysis screened out two CA-IMT-related factors, namely the disease duration and the drug administration duration were positively correlated with the average CA-IMT. The epileptic patients with disease course of more than 3 years had much higher average CA-IMT than that of the epileptics with ≤3 years disease (P < 0.001). The average CA-IMT of the patients with VPA-administration duration >1 year was also higher than that of the patients with VPA-administration duration <1 year, while the difference was not statistically significant (P = 0.196).

Conclusions: The average CA-IMT of the epileptic patients treated with VPA was higher than that of healthy people.

KEY WORDS: Atherosclerosis, Epilepsy, the carotid artery intima-media thickness, Valproate

Introduction

Atherosclerosis (AS) is the common pathological basis of various cardiocerebral diseases that has a high incidence of mutilation and mortality.[1] Epilepsy is one of the most common neurological diseases, with the incidence of 0.5–1% in global population.[2] Most epileptics require long-term or even lifelong antiepileptic drugs. In recent years, there has been a focus on the relationship between the epilepsy and AS. Studies have found that the epileptics exhibit high risk of cardiovascular events than the normal population.[3-6] This might be associated with the long-term use of antiepileptic drugs that may cause AS. No matter the conventional or new antiepileptic drugs, they all exhibit the risk that would lead to the dyslipidemia and AS.[6-9]

Valproate (VPA) is a broad-spectrum antiepileptic drug, exhibiting good effects toward the absence seizures, generalized tonic-clonic seizures, myoclonus, infantile spasm, and central benign epilepsy of children, and also having a certain effect on the partial seizures. The drug has a wide range of side effects, including metabolic or endocrine disorder, behavioral or mental problems, and idiosyncratic reaction.[10,11]

In circulation system, antiepileptic drugs cause serum homocysteine increase and changes in folic acid, lipoprotein, and uric acid levels, and has been confirmed to correlate with increased risk of AS.[12-13] During the AS formation, carotid artery intima-media thickness (CA-IMT) would appear first and then develop into atherosclerotic plaque with the prolonged disease. AS is a systemic disease, the position of CA is relatively superficial, and would be easily detected by the surface ultrasonic testing, and it is the window that could reflect the systemic atherosclerotic lesions, while currently, the B ultrasound is the only dynamic, real-time, non-destructive method that could observe and measure CA-IMT. CA-IMT could
reflect the scopes and extents of atherosclerotic lesions to some extent. The ultrasonic detection of CA-IMT is clinically performed to predict early AS. Therefore, this study was performed to test CM-IMT, thus reflecting the occurrence, development or regression of AS, and providing the basis and efficacy evaluation criteria toward the prevention and treatment of AS.

Materials and Methods

Thirty patients, including 15 males and 15 females aged 15–30 years, who received VPA therapy for at least 6 months in Department of Neurology in the Second Affiliated Hospital of Nanchang University, between September 2008 and September 2009 were diagnosed with idiopathic epilepsy through electroencephalogram and imaging combined with clinical manifestation. Thirty-three controls, including 16 males and 17 females aged 15–30 years were selected from healthy interns, graduate students, and staff members in the hospital. There were no distinct differences in gender, age, body mass index (BMI), and daily fat intake between two groups. Patients with a history of smoking, alcohol drinking, hypertension, other chronic diseases, and family history of AS, patients who previously took other antiepileptic drugs were excluded. The study was conducted in accordance with the declaration of Helsinki with approval from the Ethics Committee of Nanchang University (Ethical No. 20100096). Written informed consent was obtained from all participants.

All the participants rested in a dark room with a consistent temperature for 15 min before the examination performed by an experienced ultrasound radiologist, who did not know the clinical manifestation and testing results of patients. Philips HDI 5000 SonoCT Color Doppler echocardiography (Royal Dutch Philips Electronics Ltd, Amsterdam) was used with ultrasound center frequency of 7.0 MHz and axial resolution of 0.1 mm. Common carotid artery (CCA) was transversely checked from internal extremity of the clavicle, and then the probe traveled alongside CCA to the brain to forward, sideward, and backward observe two-dimensional real-time image of transverse and longitudinal axis of bilateral CA. CCA was observed transversely and longitudinally; longitudinal ultrasound images of the posterior wall was characterized by two parallel lines separated by a hypoechoic space, interior-line corresponding to the boundary between intima and lumen, and exterior-line corresponding to the boundary between media and adventitia; the vertical distance between them was IMT. Images at 1 cm below carotid sinus were acquired, and bilateral IMT was measured three times to calculated average CA-ITM. Body height and weight were also measured by designated person.

Statistical Analysis

Data were analyzed with SPSS 12.0 (version 12.0; SPSS, Beijing, China) and presented as X ± S. Independent-samples t-test was employed (≈ =0.05); multivariate analysis used stepwise multiple regression. Inclusion and exclusion criteria were P < 0.05 and P > 0.10, respectively.

Results

General Information

A total of 63 participants was included. There was no statistical difference in gender, age, BMI, and average daily cholesterol intake between patients and controls [Table 1]. Majority of epileptics were diagnosed as generalized tonic-clonic seizure (20), two cases of complex partial seizure and eight of complex partial seizure with secondary generalized tonic-clonic seizure; the duration of epilepsy was 7.3 ± 7.2 (0.58–22) years. A significant high bilateral CA-IMT and average CA-IMT was observed in epileptic patients as compared to the control group (P < 0.001) [Table 2].

Relation Between Disease Duration and Drug Administration

Stepwise multiple regression analysis of effects of various risk factors (age, gender, BMI, course of disease, drug exposure duration, and total dose) on CA-IMT was performed and the regression equation was Y = 0.399 + 0.007 × course of disease + 0.002 × drug exposure duration (P < 0.001). The corrected coefficients of determination were 0.468 in model 1 with course of disease as a variable and 0.506 in model 2 with course of disease and drug exposure duration as variables, showing higher proportion of explained variation over the total variation after new variable introduction [Table 3], which indicated that CA-IMT positively and linearly correlated with course of disease and drug exposure duration, that is, the longer the course of disease and drug exposure duration, the higher the CA-IMT.

Duration of Valproate Treatment

The patients were divided into subgroups according to the course of the disease ≤3 years and >3 years or VPA exposure ≤1 year and >1 year. It was observed that average CA-IMT was high in patients with longer course of disease and VPA exposure duration, but the significance was only observed in patients with course of disease ≤3 years and >3 years (P < 0.001), but not between patients with VPA exposure ≤1 year and >1 year (P = 0.196).

Table 1:

| Group     | n   | Age (years) | Gender (male/female) | BMI (kg/m²) |
|-----------|-----|-------------|----------------------|-------------|
| Epileptic | 30  | 21.90±3.680 | 15/15               | 21.39±2.580 |
| Control   | 33  | 22.00±3.562 | 16/17               | 20.56±1.699 |
| t         | -   | 0.110       | -0.118              | -1.509      |
| P         | -   | 0.913       | 0.906               | 0.137       |

BMI=Body mass index

Table 2:

| Group     | n   | Left CA-IMT (mm) | Right CA-IMT (mm) | Average CA-IMT (mm) |
|-----------|-----|-----------------|-------------------|---------------------|
| Epileptic | 30  | 0.48±0.08       | 0.50±0.08         | 0.49±0.08           |
| Control   | 33  | 0.37±0.06       | 0.39±0.05         | 0.39±0.05           |
| t         | -   | −5.253          | −5.479            | −5.85               |
| P         | -   | 0.001*          | 0.001*            | 0.001*              |

*P<0.001, as compared to the control group CA-IMT and average CA-IMT.
| CA-IMT|=Carotid artery intima-media thickness
**Blood Lipid Levels**

Compared with the control group, triglyceride of the disease group increased (1.37 ± 0.33 compared 1.040.38, P < 0.01), the AS-induction rate total cholesterol/high-density lipoprotein cholesterol (TC/HDL-c) (3.83 ± 0.89 ratio 3.05 ± 0.50, P < 0.001) and low-density lipoprotein cholesterol (LDL-c)/HDL-c (2.21 ± 0.82 ratio 1.84 ± 0.48, P < 0.05) also increased, while HDL-c (1.17 ± 0.30 ratio 1.34 ± 0.23, P < 0.05) decreased, and the differences were significant, while the difference of TC (4.25 ± 0.62 ratio 4.03 ± 0.54, P > 0.05) and LDL-c levels (2.42 ± 0.64 ratio 2.42 ± 0.55, P > 0.05) of the two groups was not statistically significant [Table 4].

**Discussion**

Currently, the incidence of asymptomatic AS in epileptics has not been reported, but research has shown that epileptics, who receive atopic eczema dermatitis syndrome (AEDs) therapy have high risk of AS and AS-related morbidity and mortality.[16-18] The relationship between CA-IMT and epilepsy is consistent, and suggests that CA-IMT is higher in epileptics taking VPA than healthy people.[19,20] IMT is an indicator for early AS and epileptics have a higher risk for AS, but whether it is induced by epilepsy or related to VPA remains unclear. A stepwise multiple regression analysis revealed that epileptics with a longer course had higher CA-IMT, indicating that increase in IMT might correlate with epilepsy. In a study on independent predictors for early AS in epileptics, Hamed et al.[23] have discovered that serum lipid peroxidation indices, such as oxidized LDL, thiobarbituric acid reactive substances and glutathione peroxidase level, are much higher in epileptics before AEDs therapy than that of control group, suggesting that epilepsy might induce IMT thickening and promote early AS by increasing lipid peroxidation.[22-24] The mechanism probably correlates with a tension state during seizure in patients, which induces cerebral angiospasm, dyspnea, hypoxia-ischemia, release of large amounts of endotoxin and significantly increased lipid peroxides. Moreover, Ca²⁺ influx and free radical-induced oxidative stress injury are observed after seizure. Excessive reactive oxygen species cause the formation of oxidized LDL particles and accelerate AS progression.

In addition, VPA has been reported to promote AS progression and increase IMT. On the one hand, the activity of glutathione peroxidase and superoxide dismutase in erythrocyte is reduced after VPA therapy, which enhances lipid peroxidation.[15] VPA treatment is always complicated by hyperinsulinemia, while insulin promotes enzyme dephosphorylation, increases the enzyme activity and facilitates cholesterol synthesis.[10] Thirdly, long-term VPA therapy induces substances that compete with cholesterol metabolism products, reduction of conversion from cholesterol to HDL-c.

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**Table 3:**

Step-wise multiple regression analysis of effects of various risk factors on CA-IMT

|                        | Model 1 |                        | Model 2 |                        |
|------------------------|---------|------------------------|---------|------------------------|
|                        | Nonstandard regression coefficient B | SE | Standard regression coefficient beta | Nonstandard regression coefficient B | SE | Standard regression coefficient beta |
| Constant term          | 0.408   | 0.009                  | -       | 0.000                  | 0.399   | 0.009                  | -       |
| Course of disease a    | 0.009   | 0.001                  | 0.690   | 0.000                  | 0.007   | 0.001                  | 0.546   |
| VPA exposure duration a| -       | -                      | -       | -                      | -       | -                      | -       |
| Gender                 | -       | -                      | -       | -                      | -       | -                      | -       |
| Age                    | -       | -                      | -       | -                      | -       | -                      | -       |
| BMI                    | -       | -                      | -       | -                      | -       | -                      | -       |
| Total dose             | -       | -                      | -       | -                      | -       | -                      | -       |
| Adjusted R²            | 0.506   | 0.468                  |         |                        |         |                        |         |
| Significance (P)       | 0.000   | 0.000                  |         |                        |         |                        |         |
| SE of the estimate     | 0.061   | 0.059                  |         |                        |         |                        |         |
| n                      | 63      | 63                     |         |                        |         |                        |         |

aThe course of disease, VPA exposure duration and total dose in control group was 0. CA-IMT=Carotid artery intima-media thickness, SE=Standard error, VPA=Valproate, BMI=Body mass index

**Table 4:**

The blood lipid levels of the two groups

| Group      | n  | TC (mmol/L) | TG (mmol/L) | LDL-C (mmol/L) | HDL-C (mmol/L) | TC/HDL-C | LDL-C/HDL-C |
|------------|----|-------------|-------------|----------------|----------------|----------|-------------|
| Control    | 33 | 4.03±0.54   | 1.04±0.38   | 2.41±0.55      | 1.34±0.23      | 3.05±0.50 | 1.84±0.48   |
| Epileptic  | 30 | 4.25±0.62   | 1.37±0.33   | 2.42±0.64      | 1.17±0.30      | 3.83±0.89 | 3.83±0.82   |
| t          | -  | −1.509      | −3.640      | −0.020         | 2.686          | −4.198   | −2.183      |
| P          |    | 0.136       | 0.001       | 0.984          | 0.009          | 0.000    | 0.034       |

P < 0.05, versus the control group, TG increased, the AS-induction rate TC/HDL-c and LDL-C/HDL-c also increased, while HDL-C decreased. P > 0.05, versus TC and LDL-c levels of the two groups. TC=Total cholesterol, TG=Triglyceride, LDL-C=Low-density lipoprotein cholesterol, HDL-C=High-density lipoprotein cholesterol, AS=Atherosclerosis
to a bile acid and bile acid release, increase in serum TC level. All of the above factors can promote AS formation. In our study, the average CA-IMT was higher in patients with VPA exposure duration >1 year than that of ≤1 year, but the difference was not significant (P = 0.196), thus whether IMT increase correlates with VPA exposure requires further investigation.

**Conclusion**

High-average CA-IMT in epileptics taking VPA than that of healthy people may correlate with epilepsy or VPA treatment, which requires large-scale prospective trials to confirm the association. AS is a multifactorial disease and CA-IMT is an important indicator for AS severity, thus CA-IMT is ultrasonically detected to diagnose early AS and simultaneously provides a basis for epileptics who take long-term AEDs whether lipid-regulating drugs or long-term monitoring of blood lipid level is required. Therefore, detection of CA-IMT is of paramount importance to reduce the incidence of AS or AS-related diseases in epileptics.

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