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Correlation Study between Genetic Polymorphisms and Blood Concentrations of Sodium Valproate in Pediatric Epilepsy Patients

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Abstract: Objective: To explore the correlation between genetic polymorphisms and blood concentrations of sodium valproate in pediatric epilepsy patients, providing evidence for individualized treatment of epilepsy patients. Methods: Pediatric epilepsy patients diagnosed with epilepsy and treated with sodium valproate monotherapy in the outpatient and inpatient departments of a tertiary hospital from January 2020 to December 2023 were selected. The steady-state blood concentrations of sodium valproate were monitored, and polymerase chain reaction (PCR) was used to genotype ABCB1G2677T/A and UGT1A6T19G genes. Data were analyzed using SPSS 17.0 statistical software. Results: The UGT1A6T19G gene polymorphism significantly affected the blood concentrations of sodium valproate in epilepsy patients. Carriers of the G allele had significantly lower blood concentrations of sodium valproate than wild-type homozygotes (TT) patients, and the decrease in blood concentrations of sodium valproate was particularly significant in homozygous mutant GG genotype patients. The ABCB1G2677T/A gene polymorphism had no statistically significant effect on the blood concentrations of sodium valproate in pediatric epilepsy patients. Conclusion: Through the study of the correlation between genetic polymorphisms and blood concentrations of sodium valproate, factors influencing the steady-state trough concentrations of valproate can be revealed from a genetic perspective, providing theoretical evidence for the precise use of sodium valproate in pediatric epilepsy patients.

Keywords: Genetic Polymorphisms; Pediatric Epilepsy; Sodium Valproate; Blood Concentration

Introduction

Sodium valproate (VPA) is a commonly used first-line broad-spectrum antiepileptic drug in clinical practice. However, VPA has a narrow therapeutic window, and there is considerable inter-individual variation among patients. Deviations of VPA blood concentrations from the normal range may lead to poor clinical efficacy or increased risk of adverse drug reactions. UDP-glucuronosyltransferases (UGT) metabolize approximately 50% of VPA in the human body. The genetic polymorphism site T19G of the major subtype UGT1A6 may alter the structure, expression, and activity of the enzyme protein, thereby playing an important role in increasing inter-individual pharmacokinetic differences of VPA among patients [1,2]. Additionally, the current conclusions regarding the correlation between the genetic polymorphism ABCB1G2677T/A and VPA blood concentrations are controversial[3,4], but its impact on VPA metabolism cannot be ignored. This study aims to explore the correlation between genetic polymorphism and VPA blood concentrations, providing reference for rational clinical drug use.

1. Methods

1.1 Study subjects

A total of 108 children with epilepsy who visited our outpatient and inpatient departments from January 2020 to December 2023 were selected as study subjects. Approval from the Ethics Committee of our tertiary hospital was obtained, and all subjects provided informed consent.

1.2 Inclusion criteria [5]

① Diagnosis of epilepsy conforms to the diagnostic criteria of the 2014 revised edition of the International League Against Epilepsy. ② Han Chinese children with epilepsy (aged <18 years) who have been taking monotherapy with sodium valproate for a long term (>2

weeks). ③ No severe hepatic or renal dysfunction, cardiovascular, gastrointestinal diseases, or severe mental disorders. ④ Good treatment compliance and complete collection of case data.

1.3 Exclusion criteria

① Non-epileptic seizures, such as psychogenic seizures or seizures caused by other reasons. ② Malignant lesions, progressive or degenerative diseases. ③ Poor treatment compliance or missing case data. ④ Long-term concurrent use of other drugs affecting valproic acid metabolism, such as carbapenem antibiotics, phenytoin, or carbamazepine. ⑤ Occurrence of severe adverse reactions.

1.4 Blood sample collection

After reaching steady-state blood drug concentrations of sodium valproate (at least 5 half-lives), 4 ml of venous blood was collected in EDTA anticoagulant tubes from the subjects 30 minutes before the next dose. After blood collection, the samples were stored in a refrigerator at -20°C, and DNA was extracted for genetic sequencing.

1.5 Genetic sequencing and typing

For the genetic sequencing and typing, the PCR amplification reaction system consisted of PCR Mix (22 μL), Primer F (10 pmol/μL, 1 μL), Primer R (10 pmol/μL, 1 μL), and DNA (1 μL). Three microliters of the PCR product were used for 1.0% agarose gel electrophoresis, and the electrophoretic patterns were photographed under UV light at 254 nm. After purification of the PCR products using magnetic beads, genetic sequencing was performed using a genetic sequencer. The Phred/Phrap software was then used for polymorphism analysis, and the analysis results were exported.

1.6 Statistical analysis

Statistical analysis was performed using SPSS 20.0 statistical software. The Hardy-Weinberg genetic equilibrium test was used to analyze the distribution of UGT1A6T19G genotypes. A P-value > 0.05 indicated that the samples included had good representativeness. Continuous data conforming to normal distribution and homogeneity of variance were expressed as mean ± standard deviation ($x \pm s$). Independent sample t-test was used for comparison between two groups, and one-way analysis of variance was used for comparison among multiple groups. Count data were expressed as cases (%), and the chi-square test was used for comparison. A P-value < 0.05 indicated a statistically significant difference.

2. Results

2.1 Comparison of standardized blood concentrations of valproic acid among different genotypes of ABCB-1G2677T/A

Among the 108 study subjects, the frequencies of GG, GT, GA, TT, TA, and AA genotypes at the ABCB1G2677T/A locus were 20%, 38%, 7%, 16%, 17%, and 3%, respectively. Single-factor analysis of variance was used to compare the standardized blood concentrations of valproic acid among the GG, GT, GA, TT, TA, and AA groups. With P > 0.05, there was no statistically significant difference in the standardized blood concentrations of valproic acid among the six genotype groups.

2.2 Comparison of standardized blood concentrations of valproic acid among UGT1A6T19G genotypes

Among the 108 study subjects, the frequencies of TT, TG, and GG genotypes at the UGT1A6T19G locus were 59%, 31%, and 10%, respectively. Single-factor analysis of variance was used to compare the standardized blood concentrations of valproic acid among the TT, TG, and GG genotype groups. With P < 0.05, there was a statistically significant difference in the standardized blood concentrations of valproic acid among the three genotype groups. Independent sample t-test was used to compare the standardized blood concentrations of valpro-

ic acid between the wild-type group (TT) and the mutant gene carrier group (TG+GG): the standardized blood concentrations of valproic acid in the (TG+GG) group were significantly lower than those in the TT group ($P < 0.05$).

3. Discussion

The effective blood concentration of valproic acid is crucial for the treatment of epilepsy, and factors influencing valproic acid metabolism in the body are numerous, complex, and exhibit significant individual differences, with genetic factors being particularly important[6]. The results of this study indicate that the UGT1A6T19G gene polymorphism significantly affects the blood concentration of valproic acid in epileptic patients. Carriers of the G allele exhibit significantly lower blood concentrations of valproic acid compared to individuals with the wild-type homozygous (TT) genotype, and the decrease in blood concentrations of valproic acid is particularly significant in patients with the homozygous mutant GG genotype. This suggests that carriers of the G allele have enhanced metabolic capacity for valproic acid in the body, resulting in lower blood concentrations of valproic acid under conventional dosing regimens. Therefore, consideration should be given to adjusting the dosage or treatment regimen accordingly. Currently, there is limited research on the correlation between ABCB1G2677T/A gene polymorphism and valproic acid blood concentration, and the conclusions are inconclusive. This study also did not find a correlation between ABCB1G2677T/A gene polymorphism and valproic acid sodium blood concentration.

4. Conclusion

Genomic research is of great significance for the individualized use of VPA. The efficacy and adverse reactions of VPA are influenced by polymorphisms in receptors, effector pathways, absorption, metabolism, and transporters. Tailoring individualized treatment plans for patients based on different genotypes, combined with blood concentration monitoring, will greatly improve the effectiveness and safety of clinical epilepsy treatment. Genetic testing may become an important predictive method for the efficacy and adverse reactions of VPA treatment for epilepsy. There is still controversy over some single nucleotide polymorphisms related to VPA, which need to be further confirmed in large samples and different populations. It is hoped that more functional genes and their polymorphic characteristics will be discovered in future research, gradually achieving precision medicine for VPA.

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