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Early Post-Traumatic Seizures are Associated with Valproic Acid Plasma Concentrations and UGT1A6/CYP2C9 Genetic Polymorphisms in Patients with Severe Traumatic Brain Injury

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Introduction

Seizure is a common complication for severe traumatic brain injury (TBI). Valproic acid (VPA) is a first-line antiepileptic drug, though its metabolism is affected by genetic polymorphisms and varies between individuals. The aim of this study was to investigate such association and to explore its influence on the occurrence of early post-traumatic seizure.

Methods

A case control study was conducted from 2012 to 2016 recruiting adult patients with severe TBI. Continuous electroencephalograph (EEG) monitoring was performed for 7 days. Genetic polymorphisms in UGT1A6, UGT2B7, CYP2C9, and CYP2C19 were analyzed in association with daily VPA plasma concentrations, adjusted dosages, and occurrence seizures.

Results

Among the 395 recruited patients, eight-three (21%) had early post-traumatic seizure, of which 30 (36.14%) were non-convulsive. Most seizures were first detected on day 1 (34.94%) and day 2 (46.99%) after injury. Patients with seizure had longer ICU length of stay and relatively lower VPA plasma concentrations. Patients with UGT1A6_19T>G/541A>G/552A>C double heterozygosities or CYP2C9 extensive metabolizers (EMs) initially had lower adjusted VPA plasma concentrations (power >0.99) and accordingly require higher VPA dosages during later time of treatment(power >0.99). The odds ratio indicated a higher risk of early post-traumatic seizure occurrence in male patients (OR 1.96, 95% CI 1.01-3.81, p=0.043), age over 65 (OR 2.13, 95% CI 1.01-4.48), and with UGT1A6_19T>G/541A>G/552A>C double heterozygosities (OR 2.38, 95% CI 1.11-5.10, p=0.02).

Conclusions

Continuous EEG monitoring are necessary to detect both convulsive and non-convulsive early post-traumatic seizures in severe TBI patients. UGT1A6/CYP2C9 polymorphisms have influence on VPA metabolism. UGT1A6_19T>G/541A>G/552A>C double heterozygositie is associated with occurrence of early post-traumatic seizures in addition to patients' age and gender. Further investigations with larger sample size are required to confirm the difference.

Learning Objectives

Continuous EEG monitoring were necessary to detect convulsive and non-convulsive post-traumatic seizures in patients with severe TBI. VPA metabolism were affected by UGT1A6/CYP2C9 mutations. It would be worthwhile to perform UGT/CYP polymorphisms screen and VPA plasma concentration monitoring within 7 days after injury. Male patients, age over 65, and with UGT1A6_19T>G/541A>G/552A>C double heterozygosities had higher risk of early post-traumatic seizures, but further investigations with larger sample size are required to better illustrate the difference.

References

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