Optimization and Evaluation of Individualized Drug Treatment Strategies in Neurological Diseases

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The popularity of personalized drug therapy in neurology is becoming more and more widespread. With the continuous development of drug monitoring and genomics, personalized therapy model has been applied to a variety of diseases. Drug monitoring refers to the detection of blood drug concentration of patients during medication, so as to adjust the medication regimen in real time. Genomics refers to the study of genetic polymorphisms in patients, including abnormalities in the function of drug-metabolizing enzymes, drug transport, and drug targets. According to the relevant reports at home and abroad, the application of the main personalized treatment methods, namely drug monitoring and genomics, in the field of neurology was summarized. The challenges and prospects of personalized medicine in the field of neurology were put forward, so as to provide better ideas for the optimization of individualized treatment in the follow-up clinical treatment.

Key words: Cerebral infarction, drug monitoring, epilepsy, genomics, neurological diseases

Neurological diseases mainly include cerebral infarction, epilepsy, neurodegenerative diseases, etc., are the main components of internal medicine. Such diseases not only affect the quality of life of patients, but also interfere with the occurrence and treatment of other diseases[1,2]. Neurological diseases are generally difficult to treat, with high severity and high mortality, so the treatment of these diseases has become an important global challenge. Studies have shown that the incidence of patients delaying the optimal treatment time due to irrational drug use is as high as 10 %, and adverse reactions caused by drug use have become an important reason for patients' treatment failure[3]. Therefore, personalized drug therapy is particularly important at present, and personalized drug therapy can be combined according to the patient's condition, genomics and lifestyle, so as to form an individualized treatment plan. Drug monitoring is a relatively late developed discipline, which refers to the real-time adjustment of patients' medication strategies according to the actual situation through the monitoring of drug blood concentration during treatment[4]. At present, anti-epileptic drugs, such as carbamazepine, valproic acid, etc., are used in the treatment of Therapeutic Drug Monitoring (TDM). The therapeutic window of such drugs is narrow and the dosage range is not large. If the dosage is exceeded, serious adverse reactions may be caused[5]. The drug monitoring treatment plan believes that blood drug concentration is related to pharmacological action and toxic reaction, rather than drug dose is related to pharmacological toxicity. For drugs with large differences between individuals, TDM is more conducive to the treatment of patients. At present, a variety of detection methods have been applied, such as enzyme-linked immunoassay and high performance liquid chromatography, which can quickly and conveniently determine the blood concentration of drugs. Valproic acid is the main drug for the treatment of epilepsy in children, which has a high global popularity and good safety, and is currently the first choice for the treatment of epilepsy. It is recommended to monitor the blood concentration during the use of this drug so that the clinical effect can be evaluated[6,7]. Due to individual differences in pediatric patients, such as height, weight, liver and kidney function, different drug administration schemes need to be developed for different pediatric patients, and individualized drug prescription is particularly important. Relevant studies have shown that the blood concentration of valproic acid is positively correlated with the dose, the higher the dose, the higher the blood concentration, and the conventional dose is 30 mg/(kg·d), at which the

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treatment effect is better. The study also found that the blood drug concentration was correlated with the age of the patient. The younger the age, the higher the blood drug concentration of the patient, but the lower the drug effectiveness. This may be due to the young age of the patient, and the difference between individuals is affected by the incomplete development of liver and kidney function, and poor compliance, resulting in large differences between individuals and low treatment effectiveness. The drug dosage form is also closely related to the blood concentration of the drug. If the drug is taken in sustained release tablets, the blood concentration is relatively stable, and the therapeutic effect is due to other oral dosage forms. It is considered that the drug in sustained release tablets has a long half-life, slow absorption and high patient compliance. At present, drug therapy for epilepsy patients is usually individualized, so as to provide a more efficient treatment basis for the safety and accuracy of drug therapy for patients[8,9]. Gene polymorphism is correlated with drug therapy effect. Pharmacogenomics is developing more and more rapidly at present, and has made great progress in the field of clinical personalized medicine, which plays an important role in the treatment of personalized medicine. Genomics refers to the analysis of gene sequences from blood or saliva so that each patient can be genotyped to specify an individualized medication regimen for a specific patient[10,11]. Genomics can also explore markers of genetic polymorphism to reduce the occurrence of adverse reactions. At present, with the rapid development of genomic detection methods, more and more high-throughput and highly sensitive technologies have begun to rise. Fluorescence *in situ* hybridization technology is an early development of technical means, this technology currently has a variety of biomarker kits, this technology is characterized by simple operation, rapid step process and high sensitivity. At present, the technology maturity of gene chip needs to be improved, but it has the advantage of high throughput. In addition, PCR technology and nucleic acid mass spectrometry technology are also developing rapidly and are constantly applied in the field of personalized medicine[12,13]. Alzheimer's disease is a chronic, progressive neurodegenerative disease with memory decline and loss of daily living ability. The pathogenesis of this disease is complex, and it is known that the abnormal expression of β-amyloid protein and Tau protein is the main pathogenic factor. At present, such diseases are mainly controlled by drug therapy, and the ultimate goal of cure cannot be achieved[14]. The treatment of Alzheimer's disease is mostly divided into ChEIs cholinesterase inhibitors and N-Methyl-D-Aspartate (NMDA) receptor antagonists. Cholinesterase inhibitors such as donepezil can delay the breakdown of acetylcholine, thus promoting cholinergic nerve transmission. NMDA receptor inhibitors such as memantine interfere with glutamate-mediated excitatory pathways[15]. In clinical application, the therapeutic effect and adverse reactions of Alzheimer's drugs vary greatly among individuals, which bring difficulties to clinical drug use. Studies have reported that drug metabolism enzymes, gene variation and other factors are the main factors leading to individual differences. The metabolizing enzyme of donepezide in the body is CYP450 enzyme, which is mainly metabolized by the CYP2D6 enzyme of this enzyme series. This enzyme can be divided into normal metabolic type (fast metabolic type), slow metabolic type, intermediate metabolic type and fast metabolic type in the body of patients. The fast metabolic type is two wild types, one gene with normal function and one partially normal gene, and this genotype accounts for the majority of patients. And it has a good therapeutic effect in the treatment. Slow metabolizers have two weakened or missing gene components, which accounts for a relatively small proportion of patients. After drug treatment, metabolism slows down and drugs accumulate, which leads to increased blood drug concentration and a high incidence of adverse reactions. Intermediate metabolic type refers to 1 wild type and 1 gene variation, and the drug metabolism rate of this type is also slow, and the treatment effect is slightly worse. Hypermetabolic type refers to abnormally fast drug metabolism, which requires increasing drug dose to lead to better therapeutic effects. Similar genetic metabolic variation occurred in the treatment of galantamine, and it was found that the drug clearance rate in patients with slow metabolism was significantly lower than that of patients with fast metabolism, and drug accumulation was easy to occur in patients with slow metabolism, so the drug dose should be reduced in actual drug use[16-18] (Table 1). Parkinson's disease is a kind of neurodegenerative disease in which nigrostriatum dopaminergic neurons are absent or Lewy bodies are formed. The clinical manifestations of this kind of disease are motor disorders and non-motor symptoms, so it is difficult and challenging to

treat in clinical treatment. Treatment for the disease is divided into drug therapy and surgical therapy, in addition to exercise, psychological or botox therapy. Drug therapy is the most common form of treatment, so there are relatively many therapeutic drugs, such as the dopamine receptor agonist pramipexole, the monoamine oxidase B inhibitor shafenamide, the Catechol-O-Methyltransferase (COMT) inhibitor entacapone, and the anticholinergic drug benzodixol. In the course of treatment, it is found that drug treatment has many differences, and different patients may have different therapeutic effects and adverse reactions after taking drugs. The variation of this type of drug is mainly caused by genetic and environmental factors. In order to reduce the variability of drug therapy, genomics also continues to play an important role in the treatment of Parkinson's disease, so as to achieve personalized treatment. The genetic sequence of each patient can be analyzed through genomics, so as to specify the most appropriate drug dosage and administration time, reducing the occurrence of low efficacy and large adverse reactions[19-21]. The genomics in Parkinson's disease is mainly concerned with dopamine receptors, dopamine metabolism and dopamine transport. There are relatively many studies on dopamine metabolic genomics, and it has been found that COMT is different in different patient genotypes, such as in Caucasian and Asian populations, the proportion of homozygous low activity genotypes is different, and the incidence rate in Caucasian is higher than that in Asian populations. Studies have shown that the difference in COMT enzyme activity is mainly due to the expression level of met gene, which can reduce the activity of COMT enzyme, thereby increasing the expression level of dopamine, further stimulating synaptic transmission, and increasing the content of dopamine in the postsynaptic membrane. For example, if the therapeutic drug levodopa acts on this target, if it has a low activity COMT genotype, the therapeutic effect is better, while if it is a carrier patient with high activity, the therapeutic effect is not good[22]. Dopamine transporter organic cationic transporter 1, which is involved in the transport of dopamine and located in chromosome 6q25, has been found through studies that the drug dose is related to the gene polymorphism of the transporter. Patients with C allele have higher drug dose[23] (Table 2). Due to the emergence of more and more monitoring means and the further exploration of disease pathogenesis, the development of personalized drug therapy in neurology is becoming more and more mature, and patient personalized therapy is becoming more and more popular. At present, new technologies such as molecular imaging technology are emerging in an endless stream, which will further promote the effectiveness of personalized medicine[24]. Of course, because of the limited understanding of the mechanism of disease and the limited understanding of genomics, personalized medicine technology needs to continue to improve, so as to continuously improve the accuracy of personalized medicine programs. Due to the emergence of more and more monitoring means and the further exploration of disease pathogenesis, the development of personalized drug therapy in neurology is becoming more and more mature, and patient personalized therapy is becoming more and more popular. 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In terms of genomics, due to the limited understanding of disease genes, the current development of genomics technology is difficult and high cost, and the subsequent research and development of genomics can be continuously increased to reduce the difficulty of detection and improve the nationwide popularity. At present, it has been reported that more and more disease gene variants are correlated with individual differences in drug effectiveness, thus providing better guidance for subsequent drug individualized therapy. By determining the clinical manifestations of genetic markers, reducing off-target therapy of gene therapy, identifying genetic variants related to drug response, and finally formulating effective individualized therapy programs.

TABLE 1: COMMON DRUG CLASSIFICATIONS FOR ALZHEIMER'S DISEASE

Mechanism	Drug
AChEI	Donepezil, galanthamine and huperzine A
NMDA	Memantine hydrochloride
Brain circulation enhancer	Nimodipine and nicergoline
GABA	Oxiracetam and piracetam
Anti-inflammatory and antioxidant	Ibuprofen and vitamin

TABLE 2: POLYMORPHISMS OF DOPAMINE SIGNALING GENES

Dopamine signaling genes	Polymorphisms
Receptor	DRD1, DRD2, DRD3, DRD4 and DRD3
Metabolic	COMT, MAOB and DDC
Transporter	OCTA and DAT

Conflict of interests:

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