Impact of ABCB1 Polymorphism on Levetiracetam Serum Concentrations in Epileptic Uygur Children in China

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Background: Interindividual variations in the efficacy of antiseizure medications make epilepsy treatment challenging. This is due to genetic factors such as gene polymorphisms in Adenosine-triphosphate (ATP)-binding cassette sub-family B member 1 (ABCB1). In this article, the impact of polymorphisms in the P-glycoprotein-encoding gene, ABCB1 (C1236T, G2677T/A, and C3435T), on levetiracetam disposition was evaluated in Uygur Chinese children with epilepsy.

Methods: MDR1 C3435T polymorphism was analyzed by polymerase chain reaction–fluorescence staining in situ hybridization. The χ² test and Fisher exact test were used to analyze the allelic and genotypic distribution of ABCB1, C1236T, G2677T/A, and C3435T between the drug-resistant and drug-responsive groups. Differences in steady-state and dose-corrected levetiracetam serum concentrations between the different genotypes were analyzed using 1-way analysis of variance and Mann–Whitney test.

Results: Total 245 Uygur children with epilepsy were analyzed [drug-resistant, n = 117 (males: females = 53:64) and drug-responsive, n = 128 (males: females = 76:52)]. The frequency of ABCB1 C1236T, G2677T/A, and ABCB1 C3435T genotypes, alleles, haplotypes, or diplotype did not differ significantly between the 2 groups (P > 0.05). Significantly higher levetiracetam concentrations and serum concentration/body mass dose were seen in ABCB1 2677-GT, TT, GA, and AT genotypes and 3435-TT carriers compared with GG and CC carriers (P = 0.021 and P = 0.002 versus P = 0.001 and P = 0.000, respectively).

Conclusions: ABCB1 G2677T/A and C3435T may affect levetiracetam disposition and therapeutic efficacy in Uygur children with epilepsy. Genetic analysis could be a valuable tool for predicting the response to antiseizure medications before the start of treatment and could contribute to personalized medicine for Uygur children with epilepsy.

Key Words: ABCB1, epilepsy, levetiracetam, serum concentration, Uygur children

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At present, no report is available on the association of ABCB1 polymorphisms with levetiracetam serum levels and treatment efficacy. This study was performed to evaluate the association of C1236T, G2677T/A, and C3435T genotypes of ABCB1 and their haplo- typic and diplotypic combinations with levetiracetam serum levels and treatment efficacy in Uygur children with epilepsy in Xinjiang, China.

MATERIALS AND METHODS
Study Participants
Between 2016 and 2019, 245 cases that met the diagnostic criteria for epilepsy were identified at the Department of Neurology and Pediatrics in People’s Hospital of Xinjiang Uygur Autonomous Region (Xinjiang, China). Patients were regularly treated with levetiracetam tablets or oral solution. The initial dose was 10 mg·kg⁻¹ daily and was increased once a week. The target dose was 20–60 mg·kg⁻¹ daily for 3–4 weeks, which was followed by blood sampling after a maintenance dose was reached. This study was approved by the Ethics Committee of People’s Hospital of Xinjiang Uygur Autonomous Region (Xinjiang, China). All study participants provided signed informed consent.

Patients were classified as drug-resistant or drug-responsive, according to the definition set by the International League Against Epilepsy. Patients were presumed to be drug-resistant if the treatment with levetiracetam was a monotherapy or in combination with other ASMs correctly prescribed for at least 12 months and at maximal tolerated doses, failed and epileptic seizures persisted. Patients were considered drug-responsive if they were totally free from seizures for at least 1 year during treatment with levetiracetam as a monotherapy or in combination with other ASMs correctly prescribed at optimal tolerated therapeutic doses.

Serum Concentration Detection
Chromatography was performed using a Waters ACQUITY UPLC BEH C18, 2.1 × 100 mm, 1.7 µm particle size column, protected by a guard column with a graphite filter. The mobile phase was a mixture of ammonium acetate solution (10 mmol/L) with acetonitrile (88:12, vol/vol). The pH of the mobile phase was set at 4.0 (with acetic acid solution). The flow rate of the mobile phases was 0.1 mL·min⁻¹, and the injection volume was 1 µL. The detection wavelength was 210 nm.

DNA Extraction and Genetic Analysis
Genomic DNA extraction was performed using a standard Qiagen kit, following manufacturer’s instructions (http://www.qiagen.com/). ABCB1 C1236T, G2677T, and C3435T were genotyped by a polymerase chain reaction (PCR) assay, using Big Dye™ (BigDye Terminator v1.1, Thermo Fisher Scientific, Waltham, MA), followed by restriction fragment length polymorphism analysis. The following forward and reverse primer sequences were designed for PCR analysis: ABCB1 rs1128503: 5’-GTTCACTTCA GTACCCCATCTCG-3’ and 5’-TCTACAT ACCATCCCCCTGTT-3’; ABCB1 rs2032582: 5’-ATTATATC CTTATATGTTGGC-3’ and 5’-TTAGAGCATAGTA A GCAGTGGGAG-3’; ABCB1 rs1045642: 5’-GTTCCTCAAG GCATAAATTATGAC-3’ and 5’-ACCCAGACTCTGTACT TGACTTAA-3’. The results of gel electrophoresis and DNA sequencing were stored as images of each genotype (Fig. 1).

Statistics
Statistical analysis was performed using SPSS version 19.0 software (version 4.0.100.1124, Chicago, IL). In addition, linkage disequilibrium (LD) analysis and haplotype construction were performed by using SHEsis online software. The χ² test was performed to compare the allelic and genotypic distribution of ABCB1 between the drug-resistant group (patient group) and the drug-responsive group (control group). Differences in steady-state and dose-corrected levetiracetam serum concentrations between different genotypes were analyzed using 1-way analysis of variance and Mann–Whitney test.

RESULTS
Characteristics of the Study Population
In this study, a total of 245 Uygur children with epilepsy (aged 1–18 years) were included, of which 129 were men and 116 were women. There were 117 drug-resistant patients, constituting the “drug-resistant group” and 128 drug-responsive patients, constituting the “drug-responsive group.” There was a statistical difference noted between the serum drug concentrations of levetiracetam and the serum concentration/body mass dose ratios (CDR) between the 2 groups. The clinical characteristics of the patients are presented in Table 1.

Genotype and Allele Frequencies of ABCB1 Single Nucleotide Polymorphisms
Hardy–Weinberg Genetic Equilibrium Test
All ABCB1 polymorphisms studied followed the Hardy–Weinberg equilibrium in drug-responsive patients (P > 0.05), which indicated that the included patients were representative of the entire group. However, in drug-resistant patients, the G2677T/A polymorphism exhibited a deviation from the Hardy–Weinberg equilibrium.

ABCB1 Genotype and Allele Frequencies
The genotype frequencies of ABCB1 C1236T did not significantly differ between the drug-resistant and drug-responsive patients with respect to CT (P = 0.087, odd ratio (OR) = 0.513, 95% confidence interval (CI) = 0.237–1.109) and TT (P = 0.166, OR = 0.576, 95% CI = 0.263–1.262) genotypes (Table 2). No significant differences were observed at the allele level (P = 0.318, OR = 0.830, 95% CI = 0.575–1.197). The genotype frequencies of ABCB1 G2677T/A did not significantly differ between drug-resistant and drug-responsive patients with respect to TT (P = 0.127, OR = 0.517, 95% CI = 0.221–1.210), GA (P = 0.255, OR = 1.011, 95% CI = 0.206–1.526), and AT (P = 0.347, OR = 0.517, 95% CI = 0.129–2.071) genotypes (Table 2). However, the GT genotype frequency of ABCB1 G2677T/A was significantly different between the drug-resistant group and the drug-responsive group (P = 0.046, OR = 0.484, 95% CI = 0.236–0.993).
The genotype frequencies of *ABCB1* C3435T did not significantly differ between drug-resistant and drug-responsive patients with respect to CT (\( P = 0.128, \text{OR} = 0.636, 95\% \text{CI} = 0.354–1.141 \)) and TT (\( P = 0.408, \text{OR} = 0.747, 95\% \text{CI} = 0.374–1.492 \)) genotypes (Table 2). No significant differences were observed at the allele level (\( P = 0.317, \text{OR} = 0.834, 95\% \text{CI} = 0.584–1.191 \)).

**Haplotype and Diplototype Association of *ABCB1* Polymorphisms**

C1236T was observed to be in strong Linkage disequilibrium (LD) with G2677T/A in the drug-resistant and drug-responsive groups (\( D' = 0.63 \) and \( D' = 0.61 \), respectively). This tight genetic linkage indicates the importance of haplotypes or multiple genetic variants from *ABCB1* for conducting phenotype–genotype correlation studies and avoiding spurious single SNP associations.

In both the drug-resistant and drug-responsive groups, all haplotypes existed, and the frequencies of each combination of *ABCB1* diplotypes were not significantly different. Table 2 shows 6 diplotype configuration frequencies above 5% in either group. Despite the minor over representation of the 5 diplotypes (CT-GT-CT, TT-GT-CT, TT-TT-TT, CT-GG-CC, CT-GT-CC, and CT-AG-CC), carriers in the drug-resistant group, and the frequencies of each combination of *ABCB1* diplotypes were not significantly different when compared with the drug-responsive group.
TABLE 1. Clinical Characteristics of Patients With Epilepsy (Mean ± SD)

| Characteristic        | Drug-Resistant Group (n = 117) | Drug-Responsive Group (n = 128) | t/χ² | P     |
|-----------------------|---------------------------------|---------------------------------|------|-------|
| Mean age ± SD, yrs    | 6.00 ± 4.57                     | 6.46 ± 6.50                     | 0.482| 0.630 |
| Gender (M/F)          |                                 |                                 |      |       |
| Male                  | 53 (45)                         | 76 (59)                         | 3.926| 0.066 |
| Female                | 64 (55)                         | 52 (41)                         |      |       |
| Body mass index, kg·m⁻²| 24.43 ± 15.26                   | 24.32 ± 15.66                   | -1.712| 0.088 |
| Dose, mg·kg⁻¹·d⁻¹     | 36.42 ± 13.55                   | 37.85 ± 12.07                   | 8.840| 0.609 |
| Steady-state plasma   |                                 |                                 |      |       |
| concentrations, µg·mL⁻¹| 12.60 ± 4.36                    | 14.09 ± 4.67                    | 6.890| 0.037*|
| CDR, µg·mL⁻¹·kg·mg⁻¹  | 0.37 ± 0.13                     | 0.40 ± 0.13                     | -21.267| <0.001*|
| Type of seizure, n (%)|                                 |                                 |      |       |
| Generalized seizure   | 101 (86)                        | 90 (70)                         | 7.459| 0.006*|
| Focal seizure         | 16 (14)                         | 38 (30)                         |      |       |
| Drugs of the last visit|                                 |                                 |      |       |
| Monotherapy           | 44 (38)                         | 75 (59)                         | 8.828| 0.003*|
| 2 drugs               | 39 (33)                         | 25 (19)                         | 4.338| 0.037 |
| 3 drugs               | 32 (27)                         | 24 (19)                         | 1.807| 0.179 |
| 4 drugs               | 2 (2)                           | 4 (3)                           | 0.205| 0.651 |

*p-value < 0.05.

Association Between ABCB1 Polymorphism and Serum Concentration of Levetiracetam

No significant difference was observed in levetiracetam concentration and CDR with respect to the ABCB1 C1236T genotype among all the patients (Table 3). However, the ABCB1 G2677T/A polymorphism significantly influenced levetiracetam concentration and CDR values. Significantly higher levetiracetam concentrations and CDR values were found in ABCB1 G2677T/A GT, TT, GA, and AT genotype carriers compared with GG carriers (P = 0.021 and P = 0.001) (Table 3). In addition, the ABCB1 C3435T polymorphism significantly influenced levetiracetam concentrations and CDR values. Significantly higher levetiracetam concentrations and CDR values were found in ABCB1 C3435T TT genotype carriers compared with CC and CT carriers (P = 0.002 and P = 0.000) (Table 3).

DISCUSSION

Epilepsy can occur at any age and its incidence peaks in the first few years of life and in the elderly. ASMs display extensive pharmacological variability between and within patients and a major determinant of differences in response to treatment is pharmacokinetic variability. These differences are attributed to genetic factors, including sex and ethnicity. However, the pharmacokinetics of ASMs can also be affected by age, specific physiological states in life, or pathological conditions.5 Levetiracetam elimination occurs primarily by renal excretion. In addition, newborns, infants older than 2–3 months, and children show higher drug clearance (normalized for body weight) than adults.31 Glauser et al32 found that the apparent clearance rate/bioavailability (CL/F) values in children and infants were comparable with those reported in children aged 6–12 years33 and higher than those reported in adults.34 Because all these factors contribute to the overall pharmacological variability in children, pharmacogenetics is only one among the many factors. The impact of pharmacogenetics testing alone is, therefore, insufficient. Serum concentrations should be monitored carefully to examine factors that result in the optimal exposure in each patient.

Several studies have shown that the correlation between MDR1 C3435T polymorphism and drug resistance in epilepsy is not completely consistent in different geographical regions and countries. In many studies, it was confirmed that the high expression of P-gp was closely related to drug resistance in epilepsy.13–19 Yu et al13 indicated that ABCB1 G2677T/A polymorphism may increase the risk of drug-resistant epilepsy in Asians. In addition, Malek et al18 reported that C1236T, G2677T, and C3435T polymorphisms were involved in ASM resistance in Tunisian patients. By contrast, some studies showed that there is no association between ABCB1 polymorphism and ASM resistance in epileptic patients.19–21 Lin et al demonstrated that there were no significant differences in the frequencies of genotypes, alleles, haplotypes, or diplotypes of ABCB1 polymorphisms between patients with drug-resistant and drug-responsive epilepsy.19 Furthermore, Lv et al21 reported that there was no significant association between the MDR1 C3435T polymorphism and overall risk of drug resistance.

Our results demonstrated no significant association between the genotypes, haplotypes, or diplotypes of C1236T, G2677T/A, and C3435T and levetiracetam resistance, which was consistent with the previous reports of Lin et al, Armond et al, and Lv et al. Discrepancies in the results of different studies may be attributed to ethnic differences in the frequencies of ABCB1 genotypes and haplotypes.
Studies have shown that \textit{ABCB1} genetic polymorphisms are associated with a high incidence of drug-resistant epilepsy, probably because polymorphisms may affect the efflux activity of transporters in endothelial cells of the blood–brain barrier, which in turn influences the concentrations of ASMs, and contributes to the failure of ASMs. In addition, several studies have indicated that \textit{ABCB1} polymorphisms may be associated with the concentrations and responsiveness of drugs such as carbamazepine, lamotrigine, oxcarbazepine, and gabapentin.\textsuperscript{24–29} Mila et al\textsuperscript{24} demonstrated that \textit{ABCB1} polymorphisms influence lamotrigine concentrations and should be considered for dose adjustment. Shen et al\textsuperscript{26} reported that the genetic polymorphism of \textit{ABCB1} rs1045642 is associated with the normalized oxcarbazepine concentration and therapeutic efficacy in patients with epilepsy (\(P < 0.05\)).

However, no report is available on the association of \textit{ABCB1} polymorphism with levetiracetam serum concentration and treatment efficacy in children with epilepsy. In the current study, we did not find any association between \textit{ABCB1} C1236T genetic polymorphism and levetiracetam serum concentrations and CDR values. However, \textit{ABCB1} C1236T, G2677T/A, and C3435T polymorphisms significantly influenced levetiracetam serum concentrations. The levetiracetam concentration and CDRs were significantly higher in \textit{ABCB1} G2677T/A GT, TT, GA, and AT genotype carriers than in GG carriers, and in \textit{ABCB1} C3435T TT, and CT genotype carriers than in CC carriers. Our findings suggest that 2677-GT, TT, GA, and 3435-TT reduce P-gp activity, promote gastrointestinal absorption of levetiracetam, and ultimately increase its serum concentration.

| SNP   | Genotype | Drug-Resistance Group, n (%) | Drug-Responsive Group, n (%) | ORs (95% CI) |
|-------|----------|-----------------------------|-----------------------------|--------------|
| C1236T | CC       | 13 (11)                     | 24 (19)                     | 0.542 (0.262–1.121) |
|       | CT       | 57 (49)                     | 54 (42)                     | 1.302 (0.786–2.156) |
|       | TT       | 47 (40)                     | 50 (39)                     | 1.047 (0.627–1.749) |
|       | C        | 83 (36)                     | 102 (40)                    | 0.830 (0.575–1.197) |
|       | T        | 151 (64)                    | 154 (60)                    |              |
| G2677T/A | GG     | 15 (13)                     | 29 (23)                     | 0.502 (0.254–0.993) |
|         | GT      | 62 (53)                     | 58 (45)                     | 1.361 (0.823–2.250) |
|         | TT      | 23 (20)                     | 23 (18)                     | 1.117 (0.588–2.122) |
|         | GA      | 12 (10)                     | 13 (10)                     | 1.011 (0.442–2.314) |
|         | AT      | 5 (4)                       | 5 (4)                       | 1.098 (0.310–3.894) |
|         | G       | 104 (45)                    | 129 (50)                    | 0.788 (0.552–1.124) |
|         | T       | 113 (48)                    | 109 (43)                    | 1.259 (0.882–1.799) |
|         | C       | 83 (36)                     | 102 (40)                    | 1.036 (0.521–2.061) |
|         | T       | 151 (64)                    | 154 (60)                    |              |
| C3435T | CC       | 32 (27)                     | 46 (36)                     | 0.671 (0.390–1.156) |
|         | CT      | 58 (50)                     | 53 (41)                     | 1.391 (0.840–2.305) |
|         | TT      | 27 (23)                     | 29 (23)                     | 1.024 (0.564–1.860) |
|         | C       | 122 (52)                    | 145 (57)                    | 0.834 (0.584–1.191) |
|         | T       | 112 (48)                    | 111 (43)                    |              |

| Haplotype | Genotype Frequencies |
|-----------|----------------------|
| CGC       | 57 (13)              | 64 (15)              |
| CGT       | 36 (8)               | 38 (9)               |
| CTC       | 36 (8)               | 38 (9)               |
| CTT       | 34 (8)               | 35 (8)               |
| TGC       | 64 (14)              | 70 (16)              |
| TGT       | 50 (11)              | 43 (10)              |
| TTC       | 58 (13)              | 50 (11)              |
| TTT       | 74 (17)              | 63 (14)              |
| Others†   | 34 (8)               | 36 (10)              |

| Diplotype | Genotype Frequencies |
|-----------|----------------------|
| CT-GT-CT  | 24 (21)              | 19 (15)              |
| TT-GT-CT  | 18 (15)              | 14 (11)              |
| TT-TT-TT  | 15 (13)              | 16 (12)              |
| CT-GG-CC  | 8 (7)                | 5 (4)                |
| CT-GT-CC  | 7 (6)                | 10 (8)               |
| Others†   | 45 (39)              | 64 (50)              |

\*P-value < 0.05.
†Haplotypes and diplotypes with total frequencies below 5% over the 2 groups.
TABLE 3. Effects of the ABCB1 Genotypes on Adjusted Levetiracetam Serum Concentrations

| SNPs       | Genotype | Number (%) | SERUM Concentration, µg·mL⁻¹ | F/Z   | P      | CDR, µg·mL⁻¹·kg·mg⁻¹ | F/t   | P      |
|------------|----------|------------|-----------------------------|-------|--------|----------------------|-------|--------|
| C1236T     | CC       | 37 (15)    | 13.64 ± 4.24                | F = 0.205 | 0.814 | 0.37 ± 0.14          | F = 0.302 | 0.740  |
|            | CT       | 111 (45)   | 13.56 ± 4.69                |       |        | 0.38 ± 0.14          |       |        |
|            | TT       | 97 (40)    | 13.29 ± 4.60                |       |        | 0.39 ± 0.12          |       |        |
|            | CT + TT  | 208 (85)   | 13.44 ± 4.64                |       |        | 0.39 ± 0.13          |       |        |
|            | versus CC|           | Z = −0.306                  | 0.760 |        | Z = −0.875           | 0.381 |        |
| G2677T/A   | GG       | 44 (18)    | 11.76 ± 3.27                | F = 2.211 | 0.068 | 0.32 ± 0.11          | F = 4.906 | 0.001* |
|            | GT       | 120 (49)   | 13.57 ± 4.40                |       |        | 0.38 ± 0.14          |       |        |
|            | TT       | 46 (19)    | 14.28 ± 5.03                |       |        | 0.43 ± 0.10          |       |        |
|            | GA       | 25 (10)    | 13.06 ± 4.66                |       |        | 0.38 ± 0.13          |       |        |
|            | AT       | 10 (4)     | 14.84 ± 7.11                |       |        | 0.45 ± 0.13          |       |        |
|            | GT + TT  | 201 (82)   | 13.76 ± 4.73                |       |        | 0.40 ± 0.13          |       |        |
|            | versus GG|           | Z = −2.310                  | 0.021* |        | Z = −3.325           | 0.001* |        |
| C3435T     | CC       | 78 (32)    | 12.63 ± 3.84                | F = 6.392 | 0.002* | 0.34 ± 0.12          | F = 17.800 | <0.001* |
|            | CT       | 111 (45)   | 12.96 ± 4.70                |       |        | 0.38 ± 0.14          |       |        |
|            | TT       | 56 (23)    | 15.24 ± 7.42                |       |        | 0.47 ± 0.09          |       |        |
|            | CT + TT  | 167 (68)   | 13.72 ± 4.81                |       |        | 0.41 ± 0.14          |       |        |
|            | versus CC|           | Z = −1.564                  | 0.118 |        | Z = −3.752           | 0.001* |        |

*P-value < 0.05 (2-sided) was considered statistically significant.

The lack of a significant association between ABCB1 C1236T, G2677T/A, and C3435T genotypes and levetiracetam resistance in our study may be attributed to several factors. First, the sample size of our study was not large enough to render sufficient power to detect a significant association. Second, there are multiple genes that could theoretically affect drug resistance in epilepsy, including the sodium channels gene (SCN1A and SCN2A). Third, it is possible that P-gp does not transport levetiracetam. Therefore, a complex induction process can be considered to be involved in the clearance of levetiracetam and drug resistance.

CONCLUSION

The findings of this study suggest that ABCB1 G2677T/A and C3435T polymorphisms may affect levetiracetam disposition and therapeutic efficacy in Uygur children with epilepsy. Thus, this study may facilitate personalized levetiracetam therapy in patients with epilepsy. Future studies, with larger cohorts, will be used for validation and to explore the underlying regulatory mechanism of action of ABCB1 genetic variations.

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