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The serum acetylcholinesterase（AChE）levels as an alternative diagnostic tool in pre－operative Hirschsprung＇s disease （https：／／www．balimedicaljournal．org／index．php／bmj／article／view／3610 ）

Dennis Chrissandy Wasito，Iskandar Ali，Fransiska Kusumowidagdo，I Gusti Bagus Adria Hariastawa
Online First：Nov 13， 2022 ｜

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Tracing management and epidemiological characteristics of close contact COVID－19 in primary health care （https：／／www．balimedicaljournal．org／index．php／bmj／article／view／3705 ）

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# Factors influencing Bromage score in post－spinal anesthesia patients 

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Clinical characteristics and mortality associated with COVID－19 in islamic hospital of Jemursari，Surabaya，Indonesia：A hospital－ based retrospective cohort study（https：／／www．balimedicaljournal．org／index．php／bmj／article／view／3541 ）

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Effect of tartrazine on blood urea nitrogen，creatinine levels，and renal tubular necrosis in adult male Wistar rats（Rattus norvegicus）：an experimental study（https：／／www．balimedicaljournal．org／index．php／bmj／article／view／3623 ）

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Evaluation of dermoscopic photoaging score among multiethnic in Medan，Indonesia（https：／／www．balimedicaljournal．org ／index．php／bmj／article／view／3810 ）

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A comparative study of full－thickness wound healing in rats using Nile tilapia skin and fresh human amnion （https：／／www．balimedicaljournal．org／index．php／bmj／article／view／3927 ）

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Distribution of blood－added tablets in adolescent girls in the COVID－19 pandemic（https：／／www．balimedicaljournal．org／index．php ／bmj／article／view／3546 ）

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Clinicopathological characteristics and possible risk factors for extrauterine metastases in endometrial carcinoma （https：／／www．balimedicaljournal．org／index．php／bmj／article／view／3820 ）

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Online First：Oct 13， 2022 ｜

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The effect of pursed－lips breathing and diaphragm exercises on the quality of life of COPD patient assessed by six－minutes walk test（https：／／www．balimedicaljournal．org／index．php／bmj／article／view／3474 ）

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Strengthening community roles to reduce stunting in COVID－19 pandemic in indonesia rural areas：capacity building program for cadres and local government（https：／／www．balimedicaljournal．org／index．php／bmj／article／view／3753 ）

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A study of molecular docking of I－tryptophan ligand as a compound in pineapples and bananas binding with the human serotonin transporter（SERT）（https：／／www．balimedicaljournal．org／index．php／bmj／article／view／3526 ）

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Fibrin glue as a novel therapy for contracted socket in comparison to mitomycin－c and triamcinolone acetonide at Dr．Soetomo General Academic Hospital，Surabaya，Indonesia（https：／／www．balimedicaljournal．org／index．php／bmj／article／view／3687 ）

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The impact of age，gender，family history of allergy，clinical symptoms，and duration of illness on flare diameter of skin prick test （https：／／www．balimedicaljournal．org／index．php／bmj／article／view／3870 ）

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Calming effect of Javanese Handwriting Calligraphy，preliminary study based on neuroaesthetics （https：／／www．balimedicaljournal．org／index．php／bmj／article／view／3598 ）

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Online First：Dec 19， 2022 ｜

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Factors related to family resilience during the COVID－19 pandemic（https：／／www．balimedicaljournal．org／index．php／bmj／article ／view／3703）

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Intensifying self－awareness of undergraduate students toward hypertension risk factors through health education （https：／／www．balimedicaljournal．org／index．php／bmj／article／view／3784 ）

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Online First：Nov 26， 2022 ｜

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Effects of probiotics and high fructose diet on De Ritis ratio，TGF－B levels，and liver histopathology of Sprague Dawley rats （https：／／www．balimedicaljournal．org／index．php／bmj／article／view／3397 ）

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Parenting stress against symptoms of gadget addiction in elementary school age during the COVID－19 pandemic （https：／／www．balimedicaljournal．org／index．php／bmj／article／view／3539 ）

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Restarting living donor kidney transplant during COVID－19：a single center experience（https：／／www．balimedicaljournal．org ／index．php／bmj／article／view／3615 ）

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Expression of $\mathrm{Na}+/ \mathrm{K}+$ ATPase and changes of corneal endothelium cell density after phacoemulsification with hypothermic perfusion（https：／／www．balimedicaljournal．org／index．php／bmj／article／view／3718 ）

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The Effect of Beta vulgaris L．on the Malondialdehyde Levels in Male Wistar Rats Exposed to Cigarette Smoke （https：／／www．balimedicaljournal．org／index．php／bmj／article／view／3806 ）

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Knowledge and parity prevention of anemia in pregnancy（https：／／www．balimedicaljournal．org／index．php／bmj／article／view／3451
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Parental support is important to improve clean and healthy living behavior for school－age children during the COVID－19 pandemic （https：／／www．balimedicaljournal．org／index．php／bmj／article／view／3544 ）

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Stromal Tumor Infiltrating Lymphocytes（TIL）as a potential prognostic biomarker for recurrence in Locally Advanced Breast Cancer（LABC）patients（https：／／www．balimedicaljournal．org／index．php／bmj／article／view／3724 ）

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Online First：Nov 21， 2022 ｜

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Application of DNA Barcoding for authentication of Balinese traditional medicinal plant Purnajiwa（Kopsia arborea Blume．and Euchresta horsfieldii）（Lesch．）Benn（https：／／www．balimedicaljournal．org／index．php／bmj／article／view／3815 ）

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A pilot study of new scoring system severity of striae distensae（https：／／www．balimedicaljournal．org／index．php／bmj／article ／view／3968）

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The effect of oral phenytoin and vitamin C therapy on enterocutaneous fistula healing（https：／／www．balimedicaljournal．org ／index．php／bmj／article／view／3469 ）

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Acceptance of the covid－19 vaccine based on health belief model（https：／／www．balimedicaljournal．org／index．php／bmj／article ／view／3549）

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The effect of Curcuma longa on fasting blood glucose，MMP－9 and IFN－y in diabetes mellitus：an experimental study （https：／／www．balimedicaljournal．org／index．php／bmj／article／view／3648 ）

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## ORIGINAL ARTICLE

Expression of Superoxide Dismutase－1（SOD－1）and changes of corneal endothelial morphology after phacoemulsification with hypothermic perfusion（https：／／www．balimedicaljournal．org／index．php／bmj／article／view／3734 ）
Afia Nuzila Fadhlina，Luki Indriaswati，Nurwasis，Dyah Fauziah，Mahmudah
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Association between the levels of muscle－specific creatinine kinase（CK－MM）and the incidence of persistent myalgia in COVID－19 survivors（https：／／www．balimedicaljournal．org／index．php／bmj／article／view／3827 ）

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Relationship between self－regulation with self－acceptance of hypertension patients during the covid－ 19 pandemic period in Indonesia（https：／／www．balimedicaljournal．org／index．php／bmj／article／view／3499 ）

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The correlation between the usage of kami pekarasa card（cards of pregnant mother for posyandu＇s members and villages authority holders）and the visit coverage of k4 pregnant mother during COVID－19 pandemic event （https：／／www．balimedicaljournal．org／index．php／bmj／article／view／3555 ）

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Ultrasound assessment of femoral cartilage thickness among healthy Indonesian adults（https：／／www．balimedicaljournal．org ／index．php／bmj／article／view／3667 ）

Rita Vivera Pane，Aisyah，Hajar Ariani，Erwien Isparnadi，Aufar Zimamuz Zaman Al Hajiri，Albert Setiawan
Online First：Dec 30， 2022 ｜

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Histopathology of colorectal cancer in Cut Meutia Hospital，Aceh－Indonesia from 2017－2020（https：／／www．balimedicaljournal．org ／index．php／bmj／article／view／3750 ）

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The performance of various laboratory parameters to differentiate follicular thyroid carcinoma and follicular thyroid adenoma （https：／／www．balimedicaljournal．org／index．php／bmj／article／view／3521 ）

Satriya Kelana，Dwi Hari Susilo，Sahudi
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Comparative effect of incentive spirometry and diaphragm breathing to functional capacity in COVID－19 patient in an isolated ward（https：／／www．balimedicaljournal．org／index．php／bmj／article／view／3579 ）

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Comparison of outcomes between a ruptured and unruptured intracranial aneurysm：results from an Indonesian cohort study （https：／／www．balimedicaljournal．org／index．php／bmj／article／view／3725 ）

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The role of serum ferritin level and disease severity in COVID－19 with type 2 diabetes mellitus patients （https：／／www．balimedicaljournal．org／index．php／bmj／article／view／3818 ）

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The effect of Quran recitation on t－cell lymphocyte activity in mice model of breast cancer（https：／／www．balimedicaljournal．org ／index．php／bmj／article／view／3473 ）

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# Relationship between CYP2C19 polymorphisms and weight gain in epilepsy patients treated with divalproex sodium: does gender matter? 

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weight gain and have focused on factors influencing the molecular pathways involved in appetite stimulation and inhibition of food satisfaction. ${ }^{10} \mathrm{CYP} 2 \mathrm{C} 19$ is one of the predominant enzymes in divalproex sodium metabolism. Three CYP2C19 genotypes were grouped in this study, namely the homozygous wild type/extensive metabolizer (EM) allele of CYP2C19* $1 / * 1$, the heterozygous intermediate metabolizer (IM) allele of CYP2C19* $1 / * 2$ or CYP2C19* $1 / * 3$ and the heterozygous poor metabolizer (PM) allele of CYP2C19* $2 / * 3$,

In the group of patients with an increased body weight, 70\% had an EM genotype while the PM population was only $5 \%$. However, in the normal or decreased weight group, the EM and PM populations were balanced (50\%). In general, the frequency of PM in Asian population is $15-25 \% .{ }^{9}$ This finding was preceded by a study, by the same researchers, that demonstrated an association between CYP2C19 polymorphisms and weight gain in patients receiving VPA. It was concluded that in women receiving VPA, body mass index ( $\mathrm{p}=0.002$ ) and weight gain ( $\mathrm{p}=0.032$ ) were higher in patients with heterozygous EM and PM CYP2C19 polymorphisms than in homozygous EM. But, in the follow-up study, the higher BMI and weight gain were found in heterozygous EM. ${ }^{9}$ Different results were also shown by a recent study that the risk of weight gain was three times higher in CYP2C19* $1 / * 2$ and CYP2C19*2/*2 than in CYP2C19* $1 /{ }^{*} 1$ of 108 VPA-treated epilepsy patients. ${ }^{19}$

The high incidence of weight gain after divalproex sodium or VPA treatment in female patients compared to male patients raises the suspicion of a different role of sex hormones in CYP2C19 gene polymorphisms and body weight by sex. Another study found an association of CYP2C19 polymorphisms with divalproex sodium, increased appetite and testosterone metabolism. ${ }^{20}$ The differences in population, genotype, study methods and other factors might affect the study results obtained. This study was conducted to determine the relationship between CYP2C19 gene polymorphisms and weight gain associated with sex, based on divalproex sodium types, daily dosage,
length of treatment, epilepsy types, family history of obesity, testosterone level and estrogen level.

## METHODS

## Study design and sample collection

This analytical cross-sectional study consisted of two sample groups and was compared simultaneously. The patients had been treated with divalproex sodium and divalproex sodium extended-release (ER) monotherapy at Airlangga University Hospital for 6 months. The subjects of this study were epilepsy patients who received valproic acid. They were selected using purposive consecutive sampling method based on inclusion and exclusion criteria. The inclusion criteria were 18-50 years old, with no history of impaired liver or kidney function, willing to participate and follow all study procedures. Specifically for the female patients, they had had regular menstrual cycles. The exclusion criteria were pregnant patients, who had a history of weight gain $>2.5 \mathrm{~kg}$ in six months before being treated with divalproex sodium and divalproex sodium ER, used hormonal contraception, corticosteroid, or herbal medicine, and followed a weight gain or loss program. From the calculation of the sample size for two populations, the total sample size was 40 patients.

## PCR-RFLP test

The materials for DNA isolation consisted of lysis buffer for cell membranes (CMLB), lysis buffer for nuclear membranes (NMLB), Tris-EDTA (TE) buffer ( 10 mM Tris HCl pH 7.4 and 0.1 mM Na2EDTA) and Tris-borate-EDTA (TBE) buffer 5x ( 54 g Trisbase, 27.5 g boric acid, 20 mL 0.5 M Na2EDTA pH 8). Primers used for polymerase chain reaction-restriction fragment length polymorphism (PCRRFLP) test was shown in Table 1.

## Genotyping

The DNA was isolated from 3 ml EDTAanticoagulated blood using an automatic gene extractor. CYP2C19 was genotyped using real-time PCR. Four reaction solutions were added to each sample according to the instruction. The internal reference probe was added to control the quality of the reaction. Each experiment was performed using a positive and a
blank control. The PCR reaction consisted of a 30 -minute hold at $37^{\circ} \mathrm{C}$, a 15 -minute hold at $95^{\circ} \mathrm{C}$, followed by 30 cycles of 30 s at $95^{\circ} \mathrm{C}, 30 \mathrm{~s}$ at $56^{\circ} \mathrm{C}$ and 45 s at $65^{\circ} \mathrm{C}$. The samples were amplified with GeneAmp PCR system 2400. When the amplification curve was obtained, the samples were analyzed using the cycle threshold value (CT-value). MyTaq HS Red Mix reagent, PCR Grade Water and primer were prepared at room temperature to amplify the genomic DNA. The remainder of the extracted DNA was stored at $2-8^{\circ} \mathrm{C}$ for 24 hours or $-70^{\circ} \mathrm{C}$ for a longer period of storage. The CYP2C19 genotypes were identified with gel electrophoresis device and gel documentation XR. The results were categorized into three groups: patients with at least two ${ }^{*} 2$ or $* 3$ alleles $(* 2 / * 2, * 2 / * 3$, or $* 3 / * 3)$ as poor metabolizers (PM), those with one ${ }^{\star} 2$ or ${ }^{*} 3$ allele $\left({ }^{*} 1 /{ }^{*} 2\right.$ or $\left.{ }^{*} 1 / * 3\right)$ as intermediate metabolizers (IM) and those without a ${ }^{*} 2$ or ${ }^{*} 3$ alleles ( ${ }^{*} 1 /{ }^{*} 1$ ) were classified as extensive metabolizers (EM).

## Estrogen level examination

Blood sample was taken before 10 a.m. and processed to be separated from serum. It was stored at room temperature (20-25 ${ }^{\circ} \mathrm{C}$ ). The blood containing precipitation was centrifuged at $10,000 \mathrm{~g}$ for less than 2 hours to avoid evaporation. Before inserting the estradiol kit reagent into the apparatus of Electrochemiluminescence Immunoassay (ECLIA), the sample was inverted 30 times and gently shaken to suspend the blood sample. The complete suspension was confirmed visually, followed by the kit reagent removal. The sample was then stored at $2-9^{\circ} \mathrm{C}$.

## Free testosterone examination

The level of testosterone was analysed using enzyme immunoassay analysis (EIA). Blood sample was taken before 10 a.m. A total of $4-5 \mathrm{~mL}$ of each serum-free blood sample was stored in a centrifuge tube at $4^{\circ} \mathrm{C}$ for 24 hours or less than $-10^{\circ} \mathrm{C}$ if it is analysed for more than 24 hours. Each calibrator, control, and specimen was pipetted $25 \mu \mathrm{~L}$ into the labelled wells. A total of $100 \mu \mathrm{~L}$ of conjugate working solution were added into each well and shaken for 10 seconds. The plate was incubated at $37^{\circ} \mathrm{C}$ for one hour. The wells
were washed three times with $350 \mu \mathrm{~L}$ of diluted wash buffer in each well and dried carefully with absorbent paper. As much as $150 \mu \mathrm{~L}$ of 3,3 ' 5,5 '-tetramethylbenzidine (TMB) substrate were pipetted into each well. The plate was incubated at $37^{\circ} \mathrm{C}$ for 10-15 minutes and pipetted $50 \mu \mathrm{~L}$ stopping solution into each well. The results were read in a microwell plate reader at 450 nm within 20 minutes.

## Statistical analysis

The association between the CYP2C19 genotypes and patients based on divalproex sodium type, dosage, duration of therapy, epilepsy types, family history
of obesity, free testosterone, estrogen level were analysed using Chi-squared test. The results were considered significant at $\mathrm{p}<0.05$. All analyses were conducted using SPSS software (NY, USA).

## RESULTS

There were 40 epilepsy patients included in this study. They were divided into two groups, patients with increased bodyweight and no increase in bodyweight group (Table 2).

The distribution of all three polymorphism groups were $60 \%(n=24)$ as EM, $37.5 \%(n=15)$ as IM and $2.5 \%(n=1)$

Table 1. Primers used in PCR-RFLP test.

| Genes | Primer | Sequence |
| :--- | :---: | :--- |
| CYP2C19*2 | Forward | 5'-CAGAGCTTGGCATATTGTATC |
|  | Reverse | 5'-GTAAACACAAAACTAGTCAATG |
| CYP2C10*3 | Forward | 5'AAATTGTTTCCAATCATTTAGCT |
|  | Reverse | 5'-ACTTCAGGGCTTGGTCAATA |

Table 2. Demographic characteristics of the included patients.

| Demographic characteristics | Total (n) | Percentage (\%) |
| :--- | :---: | :---: |
| Gender |  |  |
| Male | 17 | 42.5 |
| Female | 23 | 57.5 |
| Age (years) |  |  |
| 18-20 (inclusion criteria >18) | 9 | 22.5 |
| $21-30$ | 6 | 15.0 |
| 31-40 | 6 | 15.0 |
| 41-50 | 18 | 45.0 |
| 51-60 | 1 | 2.5 |
| Epilepsy type |  |  |
| General | 19 | 47.5 |
| Focal | 20 | 50.0 |
| Absence | 1 | 2.5 |
| Divalproex sodium type | 20 |  |
| Divalproex sodium | 20 | 50.0 |
| Divalproex sodium ER (extended release) |  | 50.0 |
| Family history of obesity | 28 | 70.0 |
| Yes | 12 | 30.0 |
| No | 20 | 50.0 |
| Weight gain | 20 | 50.0 |
| Yes |  |  |
| No |  |  |

## Table 3. Distribution of CYP2C19 polymorphisms based on gender of the patients.

| Gender | CYP2C19 polymorphism |  |  |
| :---: | :---: | :---: | :---: |
|  | *1/*1 (EM) | *1/*2 and *1/*3 (IM) | *2/*3 (PM) |
| Male | 11 (27.5\%) | 6 (15\%) | 0 (0\%) |
| Female | 13 (32.5\%) | 9 (22.5\%) | 1 (2.5\%) |
| Total | 24 (60\%) | 15 (37.5\%) | 1 (2.5\%) |

as PM. In male patients, the EM group was 11 (27.5\%) and the IM group was 6 (15\%). The EM group was 13 (32.5\%) and the IM group was 9 (22.5\%) in female patients. The IM and PM groups were mostly found in female group (Table 3).

The relationship analysis between CYP2C19 polymorphisms and sample variables (divalproex sodium types, dosage, length of treatment, epilepsy types, family history of obesity, free testosterone and estrogen level) is presented in Table 4. We found no significant relationship in CYP2C19 polymorphisms towards both of patients groups, in terms of divalproex sodium type (male vs. female, $\mathrm{p}=0.162$ vs $\mathrm{p}=0.414$ ), length of treatment (male vs. female, $\mathrm{p}=1.000$ vs $\mathrm{p}=0.478$ ) and family history of obesity (male vs. female, $\mathrm{p}=0.640$ vs $\mathrm{p}=1.000$ ).

## DISCUSSION

There were 40 patients included in this study. Based on Table 2, the patients were mostly female (57.5\%) with the age ranging between 41 and 50 years ( $45 \%$ ). They were almost equally distributed to generalized epilepsy (47.5\%) and focal epilepsy (50\%). During divalproex sodium therapy, women with generalized epilepsy are vulnerable to anovulatory cycles, polycystic ovaries and obesity. ${ }^{21}$ A significant rise of testosterone level is especially noticeable in women who begin treatment at less than 20 years, suggesting that young female epilepsy patients are at higher risk to the effects of divalproex sodium. ${ }^{22}$

Based on observations and interviews, $70 \%$ of the patients had a family history of obesity. It may cause other family members to be more likely to be obese and gain weight due to divalproex sodium consumption. ${ }^{23,24}$ this study suggested no significant relationship between family history of obesity and the CYP2C19 in causing increased body weight of divalproex sodium-treated patients.

Reproductive hormones, like testosterone and estrogen, are important modulators of energy balance and food intake. ${ }^{25}$ CYP2C19 has been linked to the metabolism of estrogen and testosterone. CYP2C19 is able to catalyze the oxidative catalysis of testosterone to produce 2 b -, 6b-, 15b-, and 16b-hydroxytestosterone. ${ }^{26}$

Table 4. Relationship of CYP2C19 polymorphism and clinical parameters in epilepsy patients based on gender.

| Parameter | Male |  |  |  | Female |  |  |  |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
|  | EM (\%) | IM (\%) | PM (\%) | $p$-value | EM (\%) | IM (\%) | PM (\%) | $p$-value |
| Divalproex sodium type |  |  |  | 0.162 |  |  |  | 0.414 |
| Divalproex sodium ER | 8 (80.0) | 2 (20) | 0 (0) |  | 4 (40) | 6 (60) | 0 (0) |  |
| Divalproex sodium | 3 (42.9) | 4 (57) | 0 (0) |  | 8 (60) | 4 (33) | 1 (7) |  |
| Dosage (mg per day) |  |  |  | 0.102 |  |  |  | 0.590 |
| 750-1500 | 5 (100) | 0 (0) | 0 (0) |  | 1 (33.3) | 1 (33.3) | 1 (33.3) |  |
| <750 | (50) | 6 (50) | 0 (0) |  | 11 (55) | 9 (45) | 0 (0) |  |
| Length of treatment (month) | 11 (64.7) | 6 (35.3) | 0 (0) | 1.000 | 12 (52) | 10 (43) | 1 (3) | 0.478 |
| Epilepsy types |  |  |  |  |  |  |  | 0.414 |
| General | 6 (75) | 2 (25) | 0 (0) | 0.620 | 7 (64) | 3 (27) | 1 (9) |  |
| Focal/Absence | 5 (55.6) | 4 (44.4) | 0 (0) | 0.620 | 5 (42) | 7 (58) | 0 (0) |  |
| Family history of obesity |  |  |  | 0.640 |  |  |  | 1.000 |
| No | 4 (57) | 3 (42.9) | 0 (0) |  | 3 (60) | 1 (20) | 1 (20) |  |
| Yes | 7 (70) | 3 (30) | 0 (0) |  | 9 (50) | 9 (50) | 0 (0) |  |
| Free testosterone |  |  |  | 0.644 |  |  |  | 1.000 |
| Normal | 7 (70) | 3 (30) | 0 (0) |  | 11 (52) | 9 (43) | 1 (5) |  |
| Increase | 1 (100) | 0 (0) | 0 (0) |  | 1 (100) | 0 (0) | 0 (0) |  |
| Decrease | 4 (66.1) | 2 (33.9) | 0 (0) |  | 0 (0) | 1 (100) | 0 (0) |  |
| Estrogen level |  |  |  | 0.515 |  |  |  | 0.090 |
| Normal | 8 (57.1) | 6 (42.9) | 0 (0) |  | 12 (6) | 7 (35) | 1 (5) |  |
| Increase | 2 (66.7) | 1 (33.3) | 0 (0) |  | 0 (0) | 2 (100) | 0 (0) |  |
| Decrease | 0 (0) | 0 (0) | 0 (0) |  | 0 (0) | 1 (100) | 0 (0) |  |

A high level of testosterone in women may cause insulin resistance and abdominal fat accumulation. ${ }^{26}$ In men, the situation appears to be exactly the contrary, with more abdominal fat is associated with lower testosterone levels. ${ }^{26}$ Estrogen may stimulate appetite and consequently cause weight gain. According to another study, CYP2C19 heterozygous EM and PM is associated with the increased level of testosterone and estrogen that induce weight gain, primarily on female epilepsy patients treated with divalproex sodium, though the actual mechanism remains unclear. ${ }^{9}$ In this study, the three CYP2C19 genotypes were mostly distributed in female patients, where EM group was 13 (32.5\%), IM group was 9 (22.5\%) and PM group was 1 patient (2.5\%) (Table 3). However, we found no significant relationship between the reproductive hormones (testosterone and estrogen) and CYP2C19 polymorphisms in inducing weight gain of divalproex sodium-treated patients, whether male or female.

Divalproex sodium inhibits the CYP2C19 to bind with a substrate which is needed to catalyze the conversion of androgens to estrogens. The inhibition
of divalproex sodium works by binding to the enzyme's active site. Consequently, when the enzyme binds to a substrate (e.g., testosterone), the enzyme becomes inactive and the androgen conversion is disrupted. ${ }^{27}$ In those with $I M$ and PM polymorphisms, the divalproex sodium will cause a lower testosterone catalysis and increase the testosterone level. The excessive testosterone level may cause a rise of appetite and body weight. ${ }^{26,28}$

The average dose of divalproex sodium ( $\mathrm{mg} /$ day) and the gender of the patients was not significantly associated. There is also no relationship between dose of divalproex sodium (mg/day) and CYP2C19 polymorphisms (Table 4). This result is different from a study in Japan that found a significant association between CYP2C19 cytochrome polymorphisms and weight gain, also a higher incidence of overweight was higher in women who lost one or two CYP2C19 alleles ( $\mathrm{p}<0.05$ ). ${ }^{9}$

Based on this study, there was no significant relationship between the CYP2C19 polymorphisms and genderbased bodyweight in epilepsy patients treated with divalproex sodium. This is similar to a previous finding that there
was no significant relationship between gender of the patients and valproic acid in inducing weight gain ( $\mathrm{p}>0.05$ ). ${ }^{9}$

## CONCLUSION

Our data suggest no association between CYP2C19 polymorphism and weight gain, in divalproex sodium-treated epilepsy patients. The result is not differed whether on male or female patients.

## ETHICAL APPROVAL

The study protocol was approved by the ethical committee of Faculty of Medicine, Universitas Airlangga, Indonesia (No. 128/EC/KEPK/FKUA/2021).

## COMPETING INTERESTS

The authors declare no conflict of interest.

## GRANT INFORMATION

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## AUTHOR CONTRIBUTION

All author had contributed in manuscript writing and agreed for the final version of the manuscript for publication.

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