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Perampanel-induced weight gain depends on level of intellectual disability and its serum concentration

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ABSTRACT

Background: Body weight (BW) gain may be induced by perampanel (PER) administration, similar to the well-known adverse effects of valproic acid and gabapentin. Intellectual disability (ID) and serum PER concentration may be risk factors of BW gain.
Purpose: This study investigated how ID and serum PER concentration are associated with PER-induced BW gain.
Methods: Subjects were 76 patients with epilepsy (41 men, aged 16–70 years). All patients were divided by intelligence quotient (IQ) into no ID (IQ ≥ 70, n = 24), mild to moderate ID (70 > IQ ≥35, n = 31), and severe to profound ID (IQ < 35, n = 21) groups. BW was measured before and 2, 4, 6, and 12 months after initiation of PER treatment, and serum PER concentration at 12 months.
Results: BW gains in the mild to moderate ID group at 4, 6, and 12 months were significantly ($p < 0.05$) higher than in the no ID and in the severe to profound ID groups. At 12 months, BW gain was associated with serum PER concentrations in the no ID ($p = 0.034$) and the mild to moderate ID ($p = 0.001$) groups but not in the severe to profound ID group. Multiple linear regression analysis found BW gain at 12 months was positively correlated with the mild to moderate ID group ($\beta = 0.373$, $p = 0.002$) and serum PER concentration ($\beta = 0.241$, $p = 0.047$).
Conclusions: The mild to moderate ID group gained more BW than the no ID group, suggesting that PER-induced food intake was greater due to weaker behavioral control in the mild to moderate ID group. The present study suggests a linear correlation between serum PER concentration and BW change.

1. Introduction

Monitoring for adverse effects of antiepileptic drugs (AEDs) as well as better seizure control improves the quality of life of both patients with epilepsy and their caregivers (Baker et al., 1997; Wheless, 2006). Body weight (BW) change is one of well-known adverse effects of some AEDs: valproic acid (VPA) and gabapentin (GBP) increase BW (DeToledo et al., 1997; Pickrell et al., 2013; Verrotti et al., 1999) whereas topiramate (TPM) and zonisamide decrease BW (Ben-Menachem et al., 2003; Lagae et al., 2015). Sustained BW gain, even if only modest, carries the risk of fatty liver, insulin resistance, and cardiovascular events (Luef et al., 2009; Pi-Sunyer, 1993; Verrotti et al., 2011). BW gain also causes poor control of blood glucose that might worsen seizure control in epilepsy patients with diabetes (Huang et al., 2008). Furthermore, AED-induced BW gain or obesity is associated with noncompliance or therapy interruption (Corman et al., 1997; Egger and Brett, 1981).

Weight change induced by AEDs is a long-term phenomenon and identification of the risk factors is important for early discovery of undesirable weight change. Intellectual disability (ID) may modify the BW changes induced by VPA and TPM (Iwaki et al., 2018; Tanamachi et al., 2015). However, little is known about whether, or how, the serum concentration of AEDs affects the BW changes. Neither daily dosage nor serum concentration of VPA is associated with BW gain (Corman et al., 1997). Higher dosage of GBP and/or TPM induces more BW change, but no relationships have been proven between weight change and serum concentrations (Ko et al., 2005; Wilding et al., 2004).

Perampanel (PER), a new AED, is the first-in-class orally active antagonist of alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionicacid (AMPA) receptors (Rogawski, 2013). Weight gain was reported as an adverse effect of PER administration (Brodie and Stephen, 2016; Singh et al., 2016). However, little is known about the factors associated with

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PER-induced BW gain. Patients with ID potentially had higher risk of PER-induced BW gain in a small case series of 12 patients with Unverricht-Lundborg disease, which is a rare disease (Crespel et al., 2017). Pooled data from phase III studies of PER showed that higher serum concentration of PER was associated with BW gain, but the relationship was not linear (Gidal et al., 2013). These two potential risk factors of PER-induced BW gain have not been fully investigated.

The present study investigated whether and how ID and serum PER concentration are associated with PER-induced BW gain.

2. Methods

2.1. Patients

This prospective, open-label, and single-center trial enrolled patients with epilepsy treated with PER for a period of 12 months at Minato Hospital outpatient clinic (Hachinohe, Aomori, Japan) from June 2016 to June 2017. Baseline BW of the patients ranged between 35 and 120 kg. All patients were prescribed at least one AED. The exclusion criteria were: limb deficiencies; history of psychiatric or mood disorders requiring major tranquilizers, antidepressants, or mood stabilizers within the past 6 months; tubal feeding; atypical eating habits due to medical conditions (e.g., eating disorders or endocrine, metabolic, hepatic, and renal disease) before the trial period; and starting TPM, VPA, or zonisamide within 12 months. Finally, a total of 108 patients (55 men and 53 women, aged 16–70 years) were included.

This study protocol was approved by the ethics committee of Minato Hospital. Informed consent, including a statement regarding the confidentiality policy, was obtained in written form from each patient and their caregivers before entry into this study. We provided patients and caregivers with the probability of PER-related BW gain. The first author takes complete responsibility for the integrity of the data and the accuracy of the data analysis.

2.2. PER titration

Indications for PER and titration were at the discretion of the treating physician. According to package inserts for Japanese PER users, physicians are recommended to initiate at a daily dosage of 2 mg and increased by 2 mg/4 weeks or slower until seizure free or intolerance is reached (maximum dose 12 mg). If a patient does not tolerate treatment during titration because of adverse effects or seizure aggravation, the dose is reduced to the previous level or treatment is discontinued.

2.3. Epileptic syndrome and mental levels

Epileptic syndrome was diagnosed according to the guidelines of the International League Against Epilepsy (Berg et al., 2010). Intelligence quotient (IQ) was evaluated by the Wechsler Adult Intelligence Scale-3rd edition or Stanford-Binet Intelligence Scales before the trial. Five mental levels were defined by IQ scores according to the Statistical Manual of Mental Disorders, 5th division criteria as follows: IQ score of 70 or over was defined as no ID, IQ score of 50–69 as mild ID, IQ score of 35–49 as moderate ID, IQ score of 20–34 as severe ID, and IQ under 19 as profound ID. The patients were divided into three groups, the no ID group, the mild to moderate ID group, and the severe to profound ID group.

2.4. Body weight change and definition of responders

The primary outcome was BW changes at 2, 4, 6, and 12 months from the baseline, which were calculated as BW at 2, 4, 6, and 12 months subtracted from baseline BW (kg).

Seizure frequencies before and after 12 months of treatment were used to determine the efficacy of PER for each patient. Responders were defined as patients experiencing 50% reduction in the frequency of all seizures. Serum PER concentrations were assessed at 12 months. Blood samples were collected at 12–16 hours after administration of PER, which occurred on the previous evening.

2.5. Data analysis

Data were processed using commercial statistical software (SPSS version 25) for Macintosh. Continuous variables are expressed as mean ± standard deviation. The significance of differences between repeated measurements such as BW change in all subjects was evaluated with one-way repeated measure analysis of variance (ANOVA). Comparisons between the no ID, mild to moderate ID, and severe to profound ID groups were performed using one-way ANOVA for continuous variables and the chi-square test for categorical variables. If significant results were found by the ANOVA or chi-square test, then the Bonferroni test was performed to identify which specific group means was different. Correlations between parameters were evaluated with the Spearman correlation test. Multiple linear regression analysis was performed to identify clinical factors related to PER-induced BW gain. Baseline variables achieving $p < 0.05$ in univariate analysis were included in the multivariable models. Statistical significance was set at $p < 0.05$ for all tests.

3. Results

3.1. Sample description

Seventy-six of the 108 patients with epilepsy who started PER treatment finally completed 12 months of treatment. A total of 30 patients withdrew from the study due to inadequate seizure control (N = 2) or adverse events (N = 28) including aggression or irritability in 11, dizziness in 10, somnolence in 4, and fall in 3.

The study population of 76 patients with epilepsy included 41 males, and mean age was 35.3 ± 14.9 years. The mean values of BW gain of all patients from the baseline were 0.7 ± 1.2 kg (1.2% of baseline) at 2 months, 1.0 ± 1.8 kg (1.8% of baseline) at 4 months, 1.6 ± 2.5 kg (2.8% of baseline) at 6 months, and 2.2 ± 3.2 kg (3.7% of baseline) at 12 months. BW changes were not observed between 2 and 4 months ($p = 0.104$), but BW at 6 and 12 months significantly increased from 2 months ($p = 0.001$ and $p < 0.001$, respectively). PER dose at 2, 4, 6, and 12 months was not correlated with BW changes at 2, 4, 6, and 12 months, respectively. Twenty-six patients (34.2%) experienced BW increases of over 5.0% at 12 months.

Table 1 compares the no ID (24 patients, 31.6%), mild to moderate ID (31 patients, 40.8%), and severe to profound ID groups (21 patients, 27.6%). Age at epilepsy onset, epilepsy syndrome, number of concomitant AEDs, co-administration of VPA, and co-administration of zonisamide showed significant differences between the three groups. The no ID group showed significantly older age at baseline compared to the mild to moderate ID group ($p = 0.021$) and the severe to profound ID group ($p = 0.017$), older age at epilepsy onset compared to the mild to moderate ID group ($p < 0.001$) and the severe to profound ID group ($p < 0.001$), lower number of concomitant AEDs compared to the severe to profound ID group ($p = 0.028$), and lower number of patients treated with VPA and zonisamide compared to the severe to profound ID group ($p = 0.012$ and $p = 0.007$, respectively).

3.2. Body weight changes and mental levels

Fig. 1 shows the BW changes throughout the 12 months of observation in each ID group. BW of the mild to moderate ID group significantly increased at 2, 4, 6, and 12 months. In contrast, the BW of the severe to profound ID group showed no significant change throughout the 12 months of observation. BW of the no ID group significantly increased at 2 and 4 months. BW gains at 2 months were not significantly

Table 1
Clinical characteristics of 76 patients who completed 12 months of PER treatment, including comparisons between no ID, mild to moderate ID, and severe to profound ID groups.

Characteristics	All patients (n = 76)	No ID (n = 24)	Mild to moderate ID (n = 31)	Severe to profound ID (n = 21)	*p* Value
Female	35 (46.0%)	13 (54.2%)	15 (48.4%)	7 (33.3%)	0.355
Age at baseline (years)	35.3 ± 14.9	43.0 ± 16.6	32.3 ± 12.9	31.0 ± 12.9	0.008*
Age at epilepsy onset (years)	13.4 ± 15.1	25.0 ± 19.4	10.8 ± 9.1	4.1 ± 6.2	< 0.001*
Duration of epilepsy (years)	22.0 ± 14.6	18.0 ± 16.7	21.6 ± 12.9	26.9 ± 13.5	0.125
Baseline BW (kg)	59.2 ± 14.2	59.4 ± 8.3	60.4 ± 11.7	57.2 ± 21.6	0.727
Height (cm)	162.2 ± 10.2	162.8 ± 10.1	163.2 ± 9.3	158.5 ± 11.1	0.225
Baseline BMI (kg/m^2)	22.5 ± 4.2	22.5 ± 3.2	22.7 ± 3.9	22.2 ± 5.5	0.094
Epilepsy syndrome					0.001*
Idiopathic generalized epilepsy	2 (2.6%)	2 (8.3%)	0 (0%)	0 (0%)	
Symptomatic partial epilepsy	70 (9.2%)	23 (91.7%)	31(100%)	16 (76.2%)	
Symptomatic generalized epilepsy	5 (6.6%)	0 (0%)	0 (0%)	5 (23.8%)	
Number of concomitant AEDs	2.9 ± 1.3	2.5 ± 1.0	2.9 ± 1.2	3.5 ± 1.4	0.030*
Baseline AED					
CBZ	42 (55.3%)	14 (58.3%)	18 (58.1%)	10 (47.6%)	0.710
TPM	42 (55.3%)	12 (50.0%)	14 (45.1%)	16 (76.2%)	0.072
LEV	35 (41.7%)	10 (41.7%)	18 (58.1%)	7 (33.3%)	0.187
CLB	24 (46.0%)	6 (25.0%)	10 (32.3%)	8 (38.9%)	0.638
VPA	22 (28.9%)	4 (16.7%)	7 (22.6%)	11 (52.4%)	0.019*
LTG	17 (22.4%)	4 (16.7%)	9 (29.0%)	4 (19.0%)	0.503
ZNS	15 (19.7%)	2 (8.3%)	4 (12.9%)	9 (42.9%)	0.007*
LCM	13 (17.1%)	4 (16.7%)	6 (19.4%)	3 (14.3%)	0.891
CZP	11 (14.5%)	3 (12.5%)	2 (6.5%)	6 (28.6%)	0.080
PHT	3 (3.9%)	2 (8.3%)	1 (3.2%)	0 (0%)	0.346
PER dose at 2 months (mg)	2.9 ± 1.0	2.8 ± 1.1	3.0 ± 1.0	3.0 ± 1.0	0.800
PER dose at 4 months (mg)	4.3 ± 2.1	4.0 ± 1.9	4.4 ± 2.2	4.7 ± 2.4	0.535
PER dose at 6 months (mg)	4.6 ± 2.6	4.2 ± 1.7	4.6 ± 2.7	5.0 ± 3.3	0.604
PER dose at 12 months (mg)	4.5 ± 2.6	4.3 ± 1.7	4.6 ± 2.7	4.8 ± 3.4	0.867
Serum PER concentration at 12 months (ng/ml)	198.5 ± 146.5	216.4 ± 147.9	217.1 ± 149.8	150.5 ± 135.7	0.219
≥50% seizure reduction	46 (60.5%)	18 (75.0%)	17 (54.8%)	11 (47.6%)	0.143

Data are the mean ± standard deviations or number (%). Significance of differences between the three groups were compared with repeated measure analysis of variance for continuous and ordinal variables and the chi-square test for categorical variables. *$p < 0.05$.
BW, body weight; BMI, body mass index; AEDs, antiepileptic drugs; PER, perampanel; CBZ, carbamazepine; TPM; topiramate; LEV, levetiracetam; CLB, clobazam; VPA, valproic acid; LTG, lamotrigine; ZNS, zonisamide; LCM, lacosamide; CZP, clonazepam; PHT, phenytoin.

different between the 3 groups, whereas BW gains in the mild to moderate ID group at 4 (1.8 ± 2.3 kg), 6 (2.9 ± 3.1 kg), and 12 months (3.8 ± 3.7 kg) were significantly higher than those in the no ID group (0.4 ± 1.3, 0.6 ± 2.0, and 1.4 ± 2.6 kg; $p = 0.010$, $p = 0.001$, and $p < 0.001$; respectively) and those in the severe to profound ID group (0.7 ± 1.0, 0.9 ± 0.9, and 0.7 ± 1.6 kg; $p = 0.007$, $p = 0.001$, and $p < 0.001$; respectively).

3.3. Body weight changes and serum PER concentrations

Fig. 2 shows the correlations between BW change and serum PER concentrations at 12 months between the three groups. PER-induced BW gain at 12 months was associated with serum PER concentration in the no ID group ($p = 0.034$, $\beta = 0.453$, $R^2 = 0.189$) and mild to moderate ID group ($p = 0.001$, $\beta = 0.552$, $R^2 = 0.304$) but not in the severe to profound ID group ($p = 0.243$).

3.4. Univariate and multivariate analysis of body weight change

Table 2 shows the results of univariate and multivariate analyses to identify factors affecting the BW change at 12 months during PER therapy. Independent variables were sex, age at baseline, age at epilepsy onset, duration of epilepsy, height, baseline BW, baseline BMI, presence of mild to moderate ID, presence of severe to profound ID, number of concomitant AEDs, co-administration of other AEDs, PER dose at 12 months, serum PER concentration at 12 months, and ≥50% seizure reduction. Univariate linear regression analysis showed BW changes were correlated with mild to moderate ID ($\beta = 0.422$, $p < 0.001$), severe to profound ID ($\beta = -0.288$, $p = 0.045$), co-administration of carbamazepine ($\beta = 0.225$, $p = 0.045$), and serum PER concentrations at 12 months ($\beta = 0.325$, $p = 0.004$). These 4 variables were assigned as independent variables for multiple linear regression analysis, which revealed that BW changes at 12 months were correlated with mild to moderate ID ($\beta = 0.373$, $p = 0.002$) and serum PER concentration ($\beta = 0.241$, $p = 0.047$).

4. Discussion

This study showed that the presence of mild to moderate ID and higher serum PER concentration were risk factors for PER-induced BW gain in patients with epilepsy. BW gain was greater in the mild to moderate ID group than in the no ID group or the severe to profound ID group. This study also identified a linear relationship between serum PER concentration and BW change by multivariate analyses. None of daily dosage, seizure reduction, or co-administration of other AEDs was significantly correlated with PER-induced BW.

Patients with lower intellectual performance experienced greater BW change but BW gain decreased in patients with severe to profound ID. This may be explained by either weaker behavior control or caregiver involvement, or both. PER-induced BW gain may involve the action of glutamatergic AMPA receptors in the nucleus accumbens on adequate food intake (Maldonado-Irizarry et al., 1995; Mietlicki-Baase et al., 2014; Peng et al., 2015). PER blocks AMPA receptors in the nucleus accumbens and may induce food intake escalation in a dose-dependent effect. In general, people with ID tend to be obese compared to people without ID because of weak control of appetite (Hoey et al., 2017; Melville et al., 2007; Mikulovic et al., 2014). In addition, patients with ID are also susceptible to behavioral change induced by PER (Crespel et al., 2017; Andres et al., 2017; Snoeijen-Schouwenaars et al., 2016). Therefore, PER-induced food intake escalation might be greater

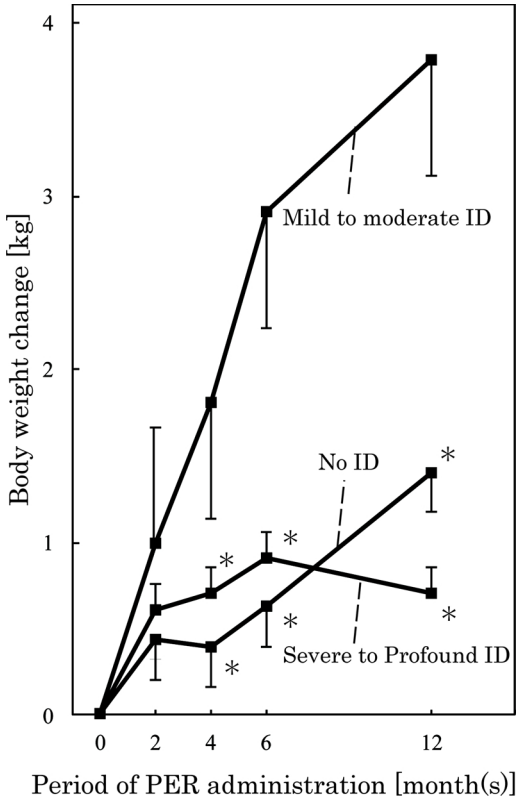

Fig. 1. Body weight changes in patient groups with different intellectual levels. Values show mean and standard error of body weight (kg). *p < 0.05 compared with the mild to moderate ID group.

due to weaker behavioral control in patients with lower intellect.

BW did not significantly change throughout 12 months and had no relationship with serum PER concentration in the severe to profound ID group. Food intake of such patients is usually controlled by caregivers either in a care facility or in the home. BW loss due to TPM was minimum in the severe to profound ID group as we reported previously (Tanamachi et al., 2015), so caregivers' control of food intake might have reduced the PER-induced BW gain in the present study.

Table 2
Factors associated with BW gain at 12 months after starting PER treatment.

Covariate	Univariate analysis	Multivariate analysis	
	p Value	β	*p* Value
Female	0.181		
Age at baseline	0.294		
Age at epilepsy onset	0.351		
Duration of epilepsy	0.910		
Height	0.863		
Baseline BW	0.565		
Baseline BMI	0.436		
Mild to moderate ID	< 0.001*	0.373	0.002*
Severe to profound ID	0.045*	−0.040	0.738
Number of concomitant AEDs	0.311		
Co-administration of other AEDs			
CBZ	0.045*	0.073	0.534
TPM	0.190		
LEV	0.762		
CLB	0.074		
VPA	0.918		
LTG	0.946		
ZNS	0.184		
LCM	0.059		
CZP	0.060		
PHT	0.403		
PER dose at 12 months	0.386		
Serum PER concentration at 12 months	0.004*	0.241	0.047*
≥50% seizure reduction	0.071		

BW, body weight; BMI, body mass index; AEDs, antiepileptic drugs; PER, perampanel; CBZ, carbamazepine; TPM; topiramate; LEV, levetiracetam; CLB, clobazam; VPA, valproic acid; LTG, lamotrigine; ZNS, zonisamide; LCM, lacosamide; CZP, clonazepam; PHT, phenytoin.

* $p < 0.05$.

PER is apparently the first AED to show a linear relationship between serum concentration and BW change, similar to other studies in which behavioral adverse effects were associated with PER dose or serum concentration (Gidal et al., 2013; Huber, 2014). In animal experiments, AMPA/kainate receptor antagonists such as 6-cyano-7-nitroquinoxaline or 6,7-dinitroquinoxaline-2, 3-dione markedly stimulated food intake and caused dose-dependent BW gain (Maldonado-Irizarry et al., 1995). Consequently, higher serum concentration of PER may escalate food intake, and linear relationships between BW gain and

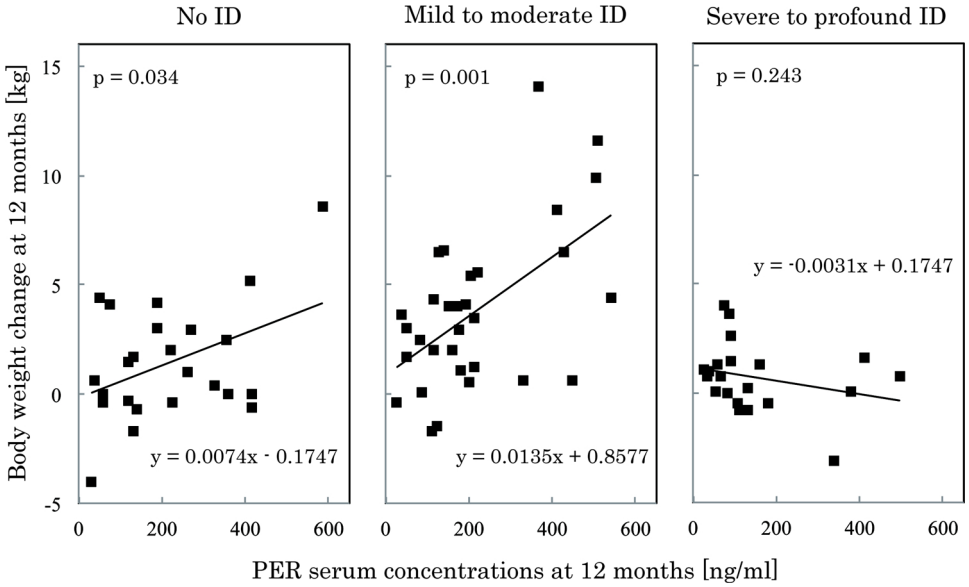

Fig. 2. Correlations between body weight changes and serum PER concentration at 12 months between the no ID, mild to moderate ID, and severe to profound ID groups.

serum PER concentration could be a distinctive feature of AMPA antagonistic actions in the nucleus accumbens. No ID group had lower risk of BW gain compared to the mild to moderate ID group, but care needs to be taken as the blood concentration of PER increases. Further prospective studies should investigate whether other AEDs show similar correlations between serum concentration and BW change.

Our present results encourage the scheduled monitoring of serum PER concentration until the maintenance dose is reached to predict adverse effects including BW gain, because serum PER concentrations are individually very variable (Yamamoto et al., 2017). PER is eliminated primarily by the hepatic metabolism via cytochrome P450 (CYP) 3A4 (Rogawski, 2013) and its metabolism is highly susceptible to interactions with AEDs that induce CYP3A4 such as carbamazepine, phenytoin, phenobarbital, and oxcarbazepine (Patsalos, 2015; Patsalos et al., 2016). Carbamazepine has been reported to decrease serum PER concentration by 67–69% and the effect of carbamazepine on serum PER concentration is stronger than other enzyme-inducing AEDs (Patsalos et al., 2016). This is probably because the co-administration of carbamazepine was associated with BW changes in univariate linear regression analysis.

Several limitations of the present study should be acknowledged. First, this is a cohort but open study of a small number of patients and short period of observation. Second, neither appetite nor amount of daily caloric intake was evaluated or controlled systematically. Third, our study lacked measures for behavioral changes such as aggression or irritability. Such behavioral adverse effects might affect BW or levels of activity. Fourth, PER-serum concentrations were not measured at 2, 4, and 6 months. However, no measurement can comprehensively cover the evaluation of behavior or mental changes for both patients with and without ID. Despite all these limitations, the present study clearly showed the pattern of BW gain during PER administration related to different intellectual levels and serum PER concentrations.

5. Conclusion

The mild to moderate ID group gained more BW than the no ID group, suggesting that PER-induced food intake was greater due to weaker behavioral control in the mild to moderate ID group. The present study suggests a linear correlation between serum PER concentration and BW change.

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Conflict of Interest

KJ has received honoraria for presentations from Daiichi Sankyo Co., Ltd., Eisai Co., Ltd., UCB Japan Co., Ltd., and Otsuka Pharmaceutical Co., Ltd. NN has received a scholarship donation from Otsuka Pharmaceutical Co., Ltd. and received a grant from Ricoh Co., Ltd. for a donated fund laboratory and received honoraria for presentations from Daiichi Sankyo Co., Ltd. and Eisai Co., Ltd. The remaining authors have no conflicts of interest. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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