

Research Article

Evaluation of Antiepileptic for Behavioral Symptoms in Severe Intellectual Disabilities

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Abstract

Antiepileptic, known to manage mood disorders, has been prescribed for behavioral symptoms in severe intellectual disabilities, but often results in multiple prescriptions.

Objective: To classify the behavioral symptoms and evaluate the prescription of antiepileptic for the extent of the behavioral symptoms.

Method: The extent of the behavioral symptoms was scored using Severe Behavior Disorder Assessment Scale, composed of the 11-items and 4-frequency scale, in 80 hospitalized subjects with severe intellectual disabilities, and analyzed in relation to the number and dose of prescribed antiepileptic. Phenytoin was prescribed for 4 subjects, and their scores were evaluated at baseline and after the prescription.

Results: The subjects with organic brain disease or epilepsy showed lower frequency of the behavioral symptoms compared to those without. Factor analysis indicated that the behavioral symptoms were classified into 3 factors; representatively, obsessive/hyperactive, aggressive and self-injurious behavior. The extent of the symptoms was inversely correlated to the number of antiepileptic, including valproic acid, carbamazepine and phenytoin. While valproic acid was significantly inversely correlated with the symptoms of obsessive/hyperactive and self-injurious behavior, phenytoin was possibly effective for the aggressive behavior. When phenytoin was prescribed in 4 subjects, the score of aggressive behavior was significantly decreased after the prescription of phenytoin, but paroxysmal tonic upgaze was often observed.

Conclusion: Valproic acid was effective for the behavioral symptoms, similarly to mood disorders, and phenytoin could stabilize the aggressive behavior. Therefore, among antiepileptic, valproic acid could be the first choice to the symptoms, and prescriptions of antiepileptic could be symptomatically selected.

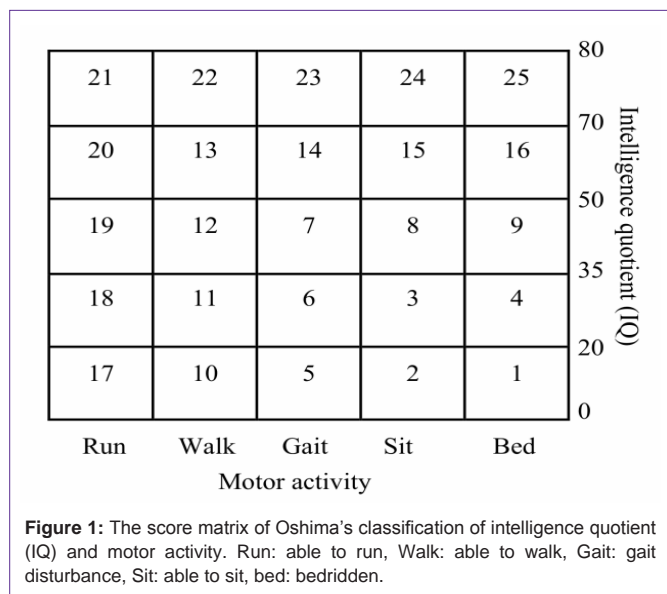
Keywords: Intellectual disabilities; Behavioral symptom; Antiepileptic; Valproic acid; Carbamazepine; Phenytoin

Introduction

Aggressive, self-injurious, and the other aberrant behaviors are troublesome in nursing and care for subjects with severe intellectual disabilities [1]. Because of resulting in self-injury and injury to their caregivers, the subjects are extremely difficult to stay at home, and necessary to intensive care in nursing home or hospital. The behavioral symptoms of the subjects, frequently and intensively acting these behaviors in the unusual manner, are symptomatically categorized as an entity called severe behavior disorder, and also synonymously “disruptive behavior disorder”, “destructive behavior”, “challenging behavior”, “aggression”, etc. Severe Behavior Disorder Assessment Scale; SBDAS has been utilized to evaluate the behavioral symptoms in Japan [2]. The total scores of the scale more than 10 were observed in 50% of inpatients admitted in national facilities for those with severe intellectual disabilities, and behavioral symptoms were more evident in those without disabled motor activity [3].

The symptoms are thought to be complicatedly caused by

genetic, brain organic, physical and circumstantial factors. Winter showed that there were significant and independent associations of challenging behavior with urinary incontinence, pain related to cerebral palsy, chronic sleep problems, and visual impairment, but not with hearing impairment, bowel incontinence, mobility impairment or epilepsy [4]. Cooper reported a cohort study to examine factors affecting aggressive behavior and self-injury in those with intellectual disabilities; aggressive behavior is correlated to lower intelligence, female, not living with family care-giver, no Down syndrome, attention-deficit hyperactivity disorders (AD/HD), and urinary incontinence, and that self-injury is the most strongly correlated to lower intelligence and AD/HD, and also correlated to no Down syndrome, not living with family care-giver and urinary incontinence [1,5]. Psychological management of the behavioral symptoms is principally the most important, but often results in care-givers exhausted. A number of studies have been undertaken with psychotropic such as antipsychotics, antiepileptic, lithium and anti depressant, and reviewed that risperidone is well demonstrated



to be effective for the behavioral symptoms [6]. Because of unwilling adverse effects, such as dizziness, fall, apathy, weight gain, the dose of antipsychotics is limited, resulting in insufficient management of the behavioral symptoms, especially aggressive behavior. The selection of prescription remains in practical experiences, and often results in multiple prescriptions.

To examine psychiatric characters of the severe behavior disorder, we evaluated and analyzed the behavioral symptoms of institutionalized subjects. To evaluate the effectiveness of antiepileptic, we also analyzed the relation between the extent of the behavioral symptoms and the number and dose of prescribed antiepileptic.

Subjects and Methods

Subjects

Subjects with severe intellectual disabilities were 80 inpatients in National Hospital Organization, Yamato Mental-Medical Center, composed of 59 males and 21 females, with their mean ± SD age of 37.6 ± 8.8 years. The causes underlying in intellectual disability were identified in 12 cases; tuberous sclerosis (2 cases), carbohydrate-deficient syndrome (2 cases), head trauma (2 cases), encephalitis (3 cases), microcephaly (1 case), fragile X syndrome (1 case) and Down syndrome (1 case), but unknown in the other 68 cases. Information of this study was given to the subjects, when possible, and their

Table 1: Type of Oshima's classification of subjects.

Classification type	Motor activity	Intelligence quotient (IQ)	Total in subjects	Percent
Type 2	Able to sit	0 - 20	1	1.25
Type 3	Able to sit	21 - 35	0	0
Type 5	Gait disturbance	0 - 20	7	8.75
Type 6	Gait disturbance	21 - 35	0	0
Type 10	Able to walk	0 - 20	25	31.25
Type 11	Able to walk	21 - 35	0	0
Type 17	Able to run	0 - 20	44	55
Type 18	Able to run	21 - 35	3	3.75

guardians, and the informed consent to participate in this study was obtained from each guardian. The study was approved by the Ethics Committee of Yamato Mental-Medical Center.

Definition of severe behavior disorder

Clinical information of the subjects was obtained from their case records, and intelligence quotient (IQ) had been evaluated by clinical psychologists using Tanaka-Binet Intelligence Scale [7] or the Enjoji developmental test that evaluates physical abilities of the whole body, skilled hand motor activities, behavior, interpersonal skills, speech ability, and language comprehension [8]. Motor and intellectual disability of each subject was evaluated for their IQ and motor activity, and classified in Oshima's classification (Figure 1) [9]. Severe behavior disorder with intellectual disabilities corresponds to type 5, 6, 10, 11, 17 and 18 in the classification, where IQ level is ranged from 0 to 35, and motor activity is normal or mildly disabled (Table 1). The total score of Severe Behavior Disorder Assessment Scale; SBDAS, abbreviated hereafter, has been shown to be correlated with all five sub-scores on the Japanese version of the Aberrant Behavior Checklist-Community (ABC-J), namely, (I) Irritability, Agitation, Crying; (II) Lethargy, Social Withdrawal; (III) Stereotypic Behavior; (IV) Hyperactivity, Noncompliance; and (V) Inappropriate Speech [10,11].

Severe behavior disorder assessment scale (SBDAS)

The information's of behavioral symptoms are obtained by interview of their care-giver, nurse, nurse teacher and medical doctor, and scored using SBDAS [2]. This instrument is composed of 11 items; self-injury, physical harm, obsessive/repetitive behavior, destruction of property, sleep problems, eating problems, toilet problems, hyperactivity, screaming, sudden agitation, and explosive violent behavior. Each itemed behavior is scored into 0 to 5 points, in accord with its frequency, where the higher point indicates the more frequent behavior (Supplement 1). The total score of SBDAS can be ranged from 0 to 55 points, and the score more than 10 points is classified as severe behavior disorder, based on the criteria defined by Ministry of Health, Labour and Welfare of Japan [2].

Epilepsy, neuroimaging, dosage of antiepileptic

Epilepsy was diagnosed by past history and EEG of all subjects, and neuroimaging study was done by brain CT or MRI. All subjects were divided into two groups by the history of epileptic attack within two years or not, and also by the existence of abnormal finding in brain neuroimaging studies. Dosage of prescribed antiepileptic was counted in each subject.

Administration of phenytoin

Four subjects were prescribed 100 mg per day of phenytoin for one week, followed by 200mg per day for 3 weeks. At baseline and after 4 weeks of the prescription, the behavioral symptoms were evaluated by care-givers using SBDAS and ABC-J scores [11].

Statistical analysis

The differences of the score of SBDAS were tested by Mann-Whitney U test, for groups divided by the history of epileptic attack, and by the existence of neuroimaging abnormality. Factor analysis was conducted against the score of 11 items of SBDAS, using principal component analysis. Correlation of the dosage of antiepileptic with

Supplement 1: Severe behavior disorder assessment scale: SBDAS.

Item	Examples of behaviors	Score 1	Score 3	Score 5
1 Self-injury	Harm itself by hitting to cut flesh or deform head, nail-peeling, etc.	1 - 2 / week	1 - 2 / day	all day long
2 Physical harm	Harm the others by biting, kicking, hitting, hair-pulling, head-butting, etc.	1 - 2 / month	1 - 2 / week	many times / day
3 Obsessive/repetitive behavior	Impossible to control the action; for example, against strong direction, take off clothes, reject to go outside, fuss over a tiny matter strongly such as coming back from long distances to pick up something, etc.	1 - 2 / week	1 - 2 / day	many times / day
4 Destruction	Break glass, furniture, door, tableware, chair, glasses, resulting in inflicting injury itself as well as the others, including tearing clothes, etc.	1 - 2 / month	1 - 2 / week	many times / day
5 Sleep problems	Days and nights being reversed, do not stay in bed and break objects or inflict troublesome on the others	1 - 2 / month	1 - 2 / week	almost every day
6 Eating problems	Cannot eat with the others, and turn over table, throw dishes, not sit down and walk around, etc. Eat feces, nail, stone, etc. Reject to eat food. Take unbalanced diet resulting in unhealthy condition.	1 - 2 / week	almost every day	almost every meal
7 Toilet problems	Play with and throw feces, slather wall with feces, repeat urination and evacuation obsessively.	1 - 2 / month	1 - 2 / week	almost every day
8 Hyperactivity	Run out incautiously and dangerously. Run around continually when not observed. Climb up a high space dangerously, for example, balcony, etc.	1 - 2 / month	1 - 2 / week	almost every day
9 Screaming	Shout intolerably. Once cry, continue to cry for several hours.	almost every day	all day long	continually
10 Sudden agitation	Once agitate, caregivers cannot calm it and cannot take care.	-	-	observed
11 Explosive violent behavior	When directed slightly, act explosively and make caregivers be afraid of it.	-	-	observed

the total score was tested by Spearman’s rank correlation, where minimum correlation efficient detectable at power 0.8 were 0.4 for valproic acid (n=48), 0.45 for carbamazepine (n=39), and 0.6 for phenytoin (n=19). The relation of dosage of antiepileptic to the score of each factor obtained was also tested by Spearman’s rank correlation. In phenytoin administration study, the scores at baseline and after 4 weeks are compared by paired t-test. P values less than 0.05 were considered significant.

Results

Factor analysis of severe behavior disorder

The subjects in this study showed mean ± SD of the total score of SBDAS at 16 ± 10.8. Among 80 subjects, at least one problem behavior was found in 73 subjects (91%), and 55 subjects (69%) were categorized as severe behavior disorder. The frequency of

Table 2: Items and factor loadings for SBDAS.

Item	Factor I	Factor II	Factor III
1 Self-injury	0.24	-0.18	0.68*
2 Physical harm	0.05	0.52*	0.62*
3 Obsessive/repetitive behavior	0.54*	0.12	-0.01
4 Destruction	0.56*	0.19	0.20
5 Sleep problems	0.79*	-0.03	0.03
6 Eating problems	0.71*	-0.04	-0.04
7 Toilet problems	0.65*	-0.21	0.12
8 Hyperactivity	0.87*	0.08	-0.14
9 Screaming	-0.04	-0.03	0.78*
10 Sudden agitation	0.06	0.85*	-0.10
11 Explosive violent behavior	0.05	0.82*	0.01
Eigenvalue	3.52	1.72	1.20
(*Factor loadings > 0.5)			

each behavior was ranked by obsessive/repetitive behavior (71.3%), hyperactivity (53.8%), self-injury (51.3%), physical harm (48.8%), eating problem (47.5%), toilet problem (40.0%), destruction (25.0%), sudden agitation (23.8%), sleep problem (22.5%), screaming (17.5%) and explosive violent behavior (10.0%). Factor analysis of each item yielded a 3-factor solution (Table 2). Factor I included obsessive/repetitive behavior, representatively, and also destruction of property, sleep problems, eating problem, toilet problems and hyperactivity. Factor II included physical harm, sudden agitation and explosive violent behavior. Factor III did self-injury, physical harm and screaming.

Neuroimaging and epilepsy

Table 3: The score of SBDAS in the groups divided by abnormality in neuroimaging.

	Abnormality in neuroimaging		Wilcoxon rank sum test
	(+)	(-)	
Number in total	40	20	
Item	Mean (SD)	Mean (SD)	p value
1 Self-injury	1.10 (1.85)	2.30 (1.69)	0.004
2 Physical harm	1.28 (1.91)	2.15 (2.23)	0.140
3 Obsessive/repetitive behavior	2.88 (2.27)	3.80 (2.04)	0.123
4 Destruction	0.63 (1.50)	1.70 (2.18)	0.024
5 Sleep problems	0.70 (1.49)	0.60 (1.44)	0.964
6 Eating problems	1.98 (2.35)	2.75 (2.55)	0.319
7 Toilet problems	1.45 (2.09)	2.15 (2.32)	0.164
8 Hyperactivity	2.20 (2.48)	3.45 (2.26)	0.055
9 Screaming	0.33 (1.12)	0.50 (0.95)	0.122
10 Sudden agitation	0.63 (1.67)	1.75 (2.45)	0.043
11 Explosive violent behavior	0.38 (1.33)	0.50 (1.54)	0.756
Total score	13.43 (10.03)	21.75 (10.94)	0.003

Table 4: The score of SBDAS in the subjects divided by the history of epilepsy.

	Epilepsy		Wilcoxon rank sum test p value
	(+)	(-)	
Number in total	22	58	
	Mean (SD)	Mean (SD)	
1 Self-injury	0.73(1.16)	1.74(1.92)	0.037
2 Physical harm	1.55(2.18)	1.74(1.98)	0.450
3 Obsessive/repetitive behavior	2.82(2.38)	3.36(2.17)	0.391
4 Destruction	0.73(1.64)	1.07(1.88)	0.346
5 Sleep problems	0.64(1.56)	0.72(1.45)	0.637
6 Eating problems	1.18(2.13)	2.48(2.41)	0.032
7 Toilet problems	0.59(1.56)	2.02(2.22)	0.005
8 Hyperactivity	1.36(2.28)	2.95(2.36)	0.010
9 Screaming	0.18(0.66)	0.41(1.08)	0.237
10 Sudden agitation	0.91(1.97)	1.29(2.20)	0.478
11 Explosive violent behavior	0.23(1.07)	0.60(1.64)	0.325
Total score	10.91(10.61)	18.40(10.28)	0.007

The group with abnormal neuroimaging findings (40 cases) showed lower total score compared to the group without (20 cases), significantly in the sub-score of self-injury and destruction of property and sudden agitation (Table 3). The group with epileptic attack within two years (22 cases) indicated lower total score compared to the group without (58 cases), significantly in the sub-score of self-injury, eating problems, toilet problems and hyperactivity (Table 4). Therefore, the subjects with organic brain disease, as a whole, showed lower frequency of behavioral symptoms.

Prescription and dosage of antiepileptic

Antiepileptic was prescribed in 67 cases, among those 34 cases had epileptic episode within 2 years. The numbers of prescribed antiepileptic were 0 (13 cases), 1 (21 cases), 2 (23 cases), 3 (14 cases), 4 (6 cases) and 5 (3 case). Among those prescribed antiepileptic, the total score of SBDAS was inversely correlated to the number of antiepileptic (Spearman’s rank correlation, $r_s = -0.32$, $p = 0.007$;

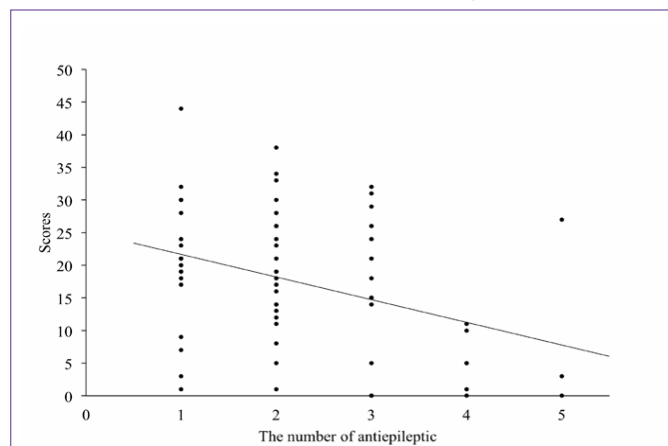


Figure 2: Scatter plot of the scores on SBDAS in the groups classified according to the number of prescribed antiepileptic. Line indicates a liner regression curve.

Figure 2). The total score of SBDAS was inversely correlated to dosage of valproic acid, but not to carbamazepine and phenytoin (Figure 3-5). Dosage of valproic acid inversely correlated significantly to 2

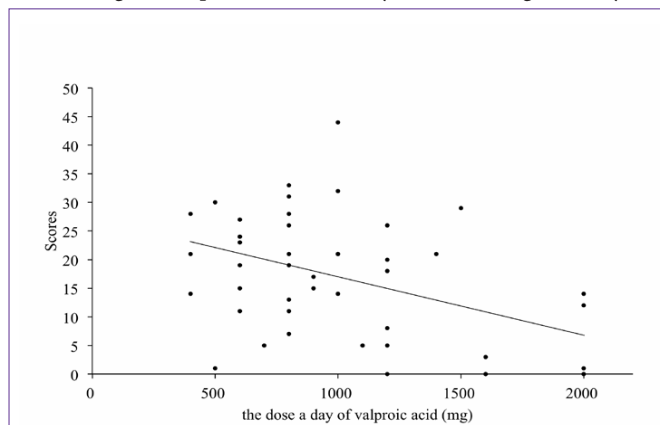


Figure 3: The relation between dosage of valproic acid and the total score of SBDAS. Line indicates a liner regression curve.

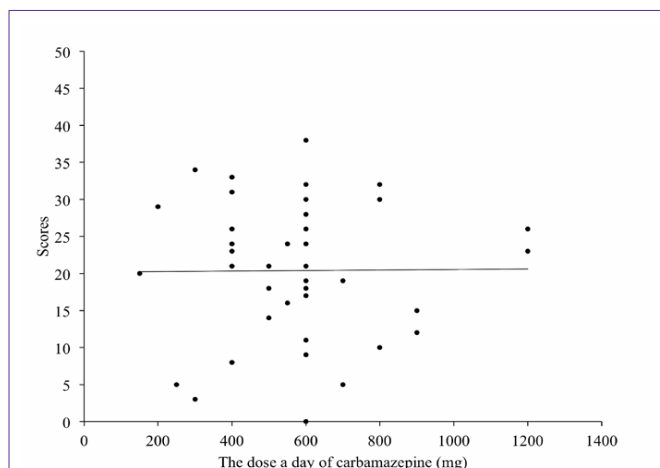


Figure 4: The relation between dosage of carbamazepine and the total score of SBDAS. Line indicates a liner regression curve.

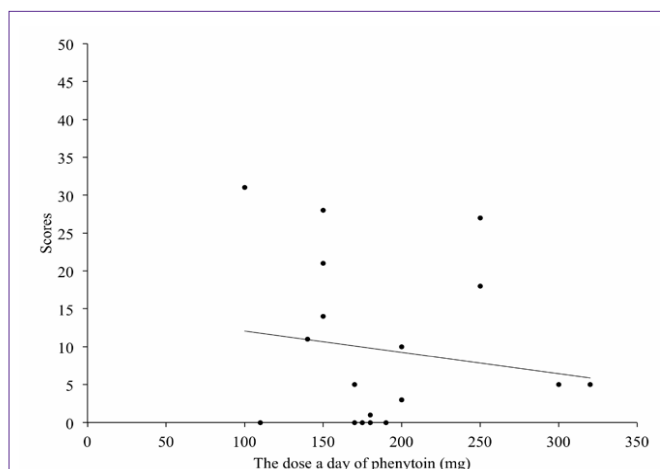


Figure 5: The relation between dosage of phenytoin and the total score of SBDAS. Line indicates a liner regression curve.

Table 5: Spearman's correlation between the dosage of antiepileptic and the score of SBDAS.

Item	Valproic acid (n=48)		Carbamazepine (n=39)		Phenytoin (n=19)	
	r_s	p	r_s	p	r_s	p
1 Self-injury	-0.56	<.0001	-0.12	0.451	-0.26	0.285
2 Physical harm	-0.18	0.232	-0.08	0.638	-0.01	0.965
3 Obsessive/repetitive behavior	-0.19	0.202	0.25	0.132	-0.20	0.413
4 Destruction	-0.07	0.620	-0.22	0.178	0.04	0.872
5 Sleep problems	-0.05	0.750	-0.21	0.202	0.28	0.244
6 Eating problems	-0.25	0.089	0.21	0.199	0.06	0.800
7 Toilet problems	-0.13	0.396	0.16	0.336	-0.44	0.059
8 Hyperactivity	-0.37	0.009	-0.05	0.745	-0.30	0.218
9 Screaming	-0.16	0.268	0.02	0.896	-0.22	0.374
10 Sudden agitation	-0.06	0.662	-0.07	0.688	-0.45	0.053
11 Explosive violent behavior	-0.01	0.960	0.07	0.659	NA	NA
12 Total score	-0.39	0.006	-0.05	0.762	-0.12	0.637

r_s , Spearman's correlation; NA, not available

Table 6: Spearman's correlation of the factors of the score of SBDAS with the dosage of antiepileptic.

	Valproic acid (n=48)		Carbamazepine (n=39)		Phenytoin (n=19)	
	r_s	p	r_s	p	r_s	p
Factor I	-0.28	0.051	-0.01	0.944	0.04	0.858
Factor II	-0.15	0.325	0.04	0.802	-0.23	0.344
Factor III	-0.45	0.001	-0.11	0.499	-0.19	0.447

r_s : Spearman's correlation
 Factor I: obsessive/repetitive behavior, destruction, sleep problems, eating problem, toilet problems, and hyperactivity
 Factor II: physical harm, sudden agitation and explosive violent behavior
 Factor III: self-injury, physical harm and screaming

sub-scales, representatively, self-injury and hyperactivity (Table 5). Dosage of phenytoin suggested a trend to inversely relate to toilet problems and sudden agitation, while carbamazepine showed no change of the total score in any dosages. When analyzed by Factors obtained by the factor analysis, dosage of valproic acid showed an inverse correlation to Factor III, and did a trend inversely to correlate to Factor I (Table 6).

Evaluation of phenytoin administration

To examine the effectiveness of phenytoin, we performed a phenytoin administration study. The score of SBDAS showed a trend to decrease by the administration of phenytoin, but not significantly (Figure 6). We also evaluated ABC-J score in 4 subjects at baseline and after 4-week administration of phenytoin. The total score after the administration was significantly decreased, and the scores of the subscale of (I) Irritability, Agitation, Crying and (II) Lethargy, Social Withdrawal were significantly lowered after the administration compared to the baseline (Figure 7). However, paroxysmal tonic upgaze was observed in 2 out of 4 subjects.

Discussion

Severe behavior disorder

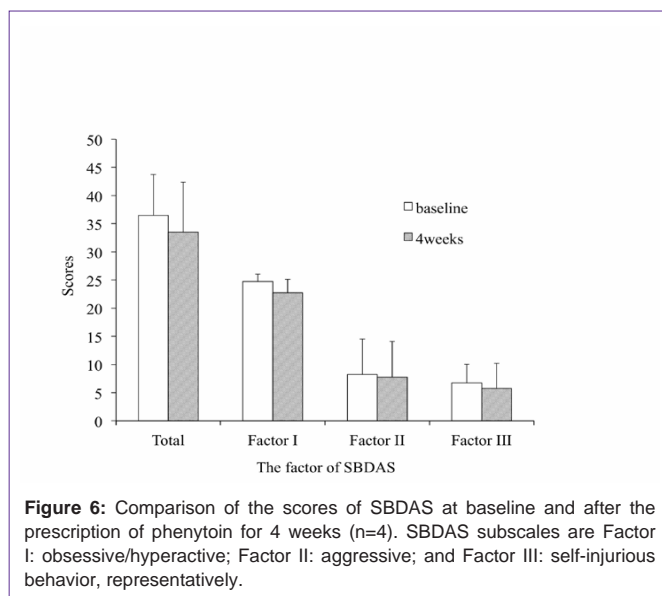


Figure 6: Comparison of the scores of SBDAS at baseline and after the prescription of phenytoin for 4 weeks (n=4). SBDAS subscales are Factor I: obsessive/hyperactive; Factor II: aggressive; and Factor III: self-injurious behavior, representatively.

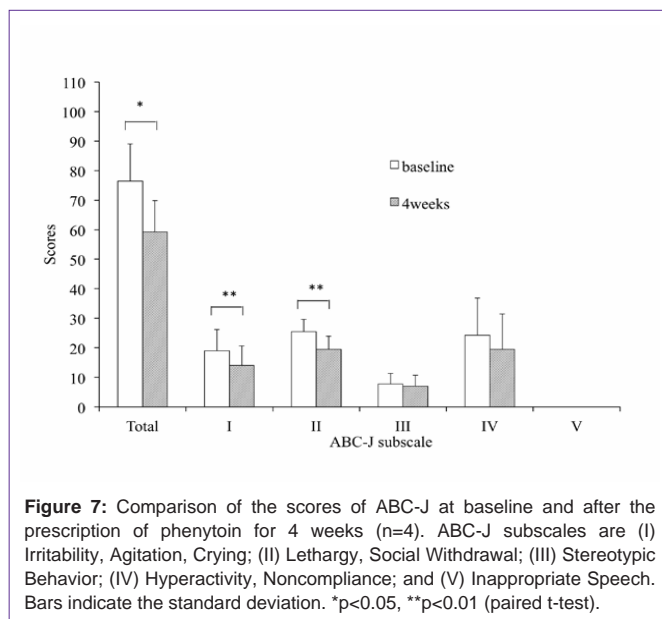


Figure 7: Comparison of the scores of ABC-J at baseline and after the prescription of phenytoin for 4 weeks (n=4). ABC-J subscales are (I) Irritability, Agitation, Crying; (II) Lethargy, Social Withdrawal; (III) Stereotypic Behavior; (IV) Hyperactivity, Noncompliance; and (V) Inappropriate Speech. Bars indicate the standard deviation. *p<0.05, **p<0.01 (paired t-test).

The prevalence of aggressive behavior with intellectual disabilities varied across studies. High frequency of behavioral symptoms in this study (91%) is caused by the selection bias of the subjects, because those were institutionalized in the wards of severe intellectual disabilities. Crocker reported that among 3165 adult with intellectual disability, aggressive behavior was found in 51.8% during 12 months, and the most frequent symptom was verbal aggression (37.6%) [12]. Poppes showed that the prevalence of self-injury and stereotypical behavior in people with profound intellectual disability was 82%, and aggressive/destructive behavior was 45% [13]. Cooper reported that the point prevalence of aggressive behavior and self-injurious behavior was 9.8% and 4.9%, respectively, among the adult population of intellectual disabilities in community-based setting in UK [1,5].

Factor analysis of the symptoms indicated that 11 classified behaviors could be grouped into 3 factors. Factor I could be encountered in daily activity and mainly caused by stereotypy, and

could represent manic symptoms. Factor II could be excitement symptoms caused by impulsive aggression. Factor III could be psychological irritation occasionally associated with agitation. Physical harm was included in both factor II and III, suggesting that physical harm could be caused by impulsive aggression or psychological irritation. Therefore, these behavioral symptoms need to be managed by appropriate prescription.

Neuroimaging and epilepsy

Subjects with no abnormal findings in neuroimaging studies showed higher total scores of SBDAS, suggesting that organic brain diseases often result in reduced behaviors possibly caused by decreased activity. Comai described in their reviews that the most important areas in the control of aggression are prefrontal cortex, and impairments of many neurotransmitter systems, including serotonin (5-HT), dopamine (DA), and norepinephrine (NE), are implicated in the biology of aggression [14]. Subjects with epileptic attack also showed lower total score in this study. Matthews reported that among 318 adults with intellectual disability from 40 general practices, there was no significant difference in challenging behavior between epilepsy and non-epilepsy groups [15]. Therefore, epilepsy, in itself, unlikely relates to the frequency of behavioral symptoms.

Prescription of antiepileptic

The number of antiepileptic was correlated to the lower total score of SBDAS in this study. There are a large number of studies in antiepileptic medication for the aggressive behavior [16-18]. Antiepileptic has potential to act as mood-stabilizer, but not consistently, possibly caused by instability of blood concentration and occurrence of unwilling side effect. We found that the dosage of valproic acid inversely correlated to the total score, significantly to the sub-score of self-injury and hyperactivity. Ruedrich reported that a compound of sodium valproate and valproic acid improved aggressive or self-injurious behavior in adults with intellectual disability [19]. Muehlmann made model animals of self-injury by administering pemoline to male Long Evans rats, showing that risperidone, valproic acid and topiramate significantly attenuate pemoline-induced self-injurious behavior, and raised a possibility that valproic acid might attenuate self-injurious behavior by inhibiting monoaminergic neurotransmission through increasing extracellular GABA concentration [20].

Phenytoin showed a trend to improve the score of toilet problems and sudden agitation in this study, though the number of subjects prescribed phenytoin was small (19 out of 80 subjects). We showed that phenytoin is effective to reduce behavioral symptoms, also sudden agitation, but the number of the subject in the administration study of phenytoin was limited in our study because of the high frequency of paroxysmal tonic upgaze. Phenytoin stabilizes effectively for patients with bipolar mania [21]. Phenytoin affects voltage-gated potassium currents [22], and when treated rats with phenytoin, the expression of genes potentially associated with mechanisms of mood regulation [23]. Phenytoin was limitedly utilized as mood-stabilizer, but has potential to design another mood-stabilizer. However, the number of subjects is small in this study and for a short period, the effectiveness of phenytoin should be evaluated in a large number of subjects by long-term evaluation. It is important to follow-up the patients by neuroimaging study to prevent them from cerebellar

atrophy and ataxia. On the other hand, our results did not support that carbamazepine is effective on behavioral symptoms, though the number of sample was quite small to detect a low effectiveness. While Stanford reported that carbamazepine was effective in treating impulsive aggression [24], Cueva showed in an double-blind and placebo-controlled study that carbamazepine was not effective in treating aggressive behavior of children with conduct disorder [25]. Therefore, carbamazepine should be carefully prescribed in multiple medications.

Conclusion

We scored the behavioral symptoms in intellectual disabilities by the scoring of SBDAS, and the symptoms can be classified to 3 Factors. Among antiepileptic, valproic acid was effective to control the symptoms of obsessive/hyperactive and self-injurious behavior. We showed that phenytoin attenuates the aggressive behavior. Because of unwilling side effect, multiple antiepileptic treatments are not recommended, and considering to the behavioral symptoms, the appropriate antiepileptic could be selected to manage behavioral symptoms in intellectual disabilities.

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