Effect of phosphatidylserine administration on symptoms of attention-deficit/hyperactivity disorder in children

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PURPOSE

To clarify whether the administration of phosphatidylserine ("PS") can improve the attention-deficit ("AD") and hyperactivity disorder ("HD") symptoms in children. with AD/HD.

STUDY DESIGN AND SUBJECTS

A pilot study in 15 AD/HD children 6 to 12 years old (including 6 suspected to have AD/HD) who had rarely received medication before. These 15 children took 200 mg/day of PS in a capsule every day for 2 months. The following items were investigated at the start of study ("pre-study") and upon completion of study ("post-study): 1) AD/HD symptoms (inattention/hyperactivity and impulsiveness) based on DSM-IV diagnostic criteria, 2) learning disorders (hearing, speaking, reading, writing, calculation, inference) based on learning disorders ("LD") check list, 3) visual perception (figure background perception task to find a prescribed form in the sheet), 4) visual and auditory short-term memory and 5) continuous performance test ("CPT").

RESULTS

After the intervention, (1) AD/HD symptoms were significantly improved ($p<0.01$). Significant improvement was observed both in the inattention and hyperactivity and impulsiveness ($p<0.01$ and $p<0.05$ respectively) (3) visual perception was also significantly improved ($p<0.001$). A tendency towards an improvement was observed in (2) LD and (5) CPT (9 only error) ($p<0.10$). However, no significant difference was observed with regard to visual and auditory short-term memory (4).

CONCLUSION

PS was shown to improve AD/HD symptoms as demonstrated by the results of DSM-IV diagnostic criteria, visual perception test, learning disorder checklist, and CPT. Further studies using larger sample sizes are required to confirm the significant beneficial results of PS on AD/HD of this pilot trial.

INTRODUCTION

Attention-deficit/hyperactivity disorder (AD/HD) is one of the most important chronic neurological diseases in childhood. AD/HD is regarded as a failure in appropriately controlling the emotional response in the frontal lobe, due to a problem of disinhibition (1). Disinhibition consists of disinhibition of attention (inattention) and that of behaviour (hyperactivity and impulsiveness).

AD/HD patients are classified into inattention-predominant type, hyperactivity and impulsiveness -dominant type and mixed type. Each symptom causes problems in learning and relation between family members. Though the cause of disorders has yet to be identified (2), central stimulants (a type of psycho stimulant) are used in the treatment. These drugs can alleviate the AD/HD symptoms to some extent (3, 4). However, there is no consensus on the long term use of these drugs and adverse events (adverse reactions) may occur during or years after the treatment (5). Accordingly, supplementary and substitute medication is frequently advised. There will be no problem if such medication is safe and effective. However, many of these treatments have not been scientifically investigated (6).

Phosphatidylserine (PS) is a naturally occurring phospholipid present in all biological membranes of animals, higher plants and micro organisms. In humans, PS is most concentrated in the brain where it comprises up to 15 percent of the total phospholipid pool. PS plays an important role in the functioning of neuronal membranes, e.g., maintenance of the neuron's internal environment, secretory vesicle release, signal transduction, cell-to-cell communication, and cell growth regulation (7-10).

Thus, it is not surprising that this phospholipid is considered to be an important brain nutrient (11). Numerous studies in animals and humans have documented effects of PS on specific neurotransmitter systems, including brain acetylcholine (12), norepinephrine (8), serotonin (13), and dopamine (14). These data indicate that PS has an effect on neurotransmitter systems that may play a role in cognitive functions. Clinical studies indeed have provided significant evidence that the central effects of an oral PS treatment have beneficial effects on cognitive functions (for a review see (15) and (16)). The only evidence available indicating that PS could serve as a supplementary and substitution treatment for AD/HD comes from a preliminary study carried out by the renowned American paediatrician Carol Ann Ryser (17). In a physician in-office study of 21 consecutive ADHD cases aged 4-19, dietary supplementation with PS benefited greater than 90 percent of these cases. At intakes of 200-300 mg/day of PS for up to four months, attention and learning were most consistently improved. However, this research has not been prepared into a formal thesis.

In the present study, 200 mg PS per day was administered for 2 months to 15 AD/HD children (including 6 suspected to have AD/HD). Most of these children (13) had rarely received any medication before, while the remaining two had been given methylphenidate hydrochloride (Ritalin®).

METHODS

Subjects

At first, 21 AD/HD children (6 - 12 years old) were recruited for this research but 6 of them dropped out. It was not possible to obtain the cooperation of family in 2 of these drop-out cases (the informed consent was acquired from both mothers but the understanding of father was not obtained for 1 of the 2 children and that of grandmother for the other). The other 4 children were not willing to take PS capsules. Nine of remaining 15 children were each diagnosed to have AD/HD on the basis of DSM-IV and diagnostic interviews including behaviour observation by the psychiatrists who were their respective attending physicians while the remaining 6 were suspected to have AD/HD. All children did exhibit an IQ level in the standard range. This study is based on data received from the remaining 15 children. The details are shown in Table 1. Informed consent was obtained from the parents of the children.

Male/female	13/2
Age (male/female)	8,11 (8,11/8,10)
Number of children already receiving medication*	2
AD/HD (including suspected cases)	15
Number of children with co morbid disorders	
AS** and HFA***	2
LD****	9

* Both children were treated with Ritalin® alone
** AS: Asperger's syndrome
*** HFA: High Function Autism
****LD: Learning Disorder

Table 1. Characteristics of children participating in the study

Capsule used in the study and administration method

The children took 2 capsules containing each 100 mg for 2 months. Phosphatidylserine Lipamin-PS 90, Cargill Food Ingredients, Germany, is a substance of food-grade quality, produced from soy lecithin by enzymatic transesterification. The product Lipamin-PS 90 contains 88 percent PS, 2 percent phosphatidylcholine (PC), 5 percent phosphatidic acid (PA) and approximately 62 percent of polyunsaturated fatty acids. Final study formulation contained 20 percent PS, 5 percent PC, 3 percent phosphatidylethanolamine (PE), 3 percent phosphatidylinositol (PI), 5 percent PA and 28 percent polyunsaturated fatty acids. Each active capsule contained a phospholipid mixture of the composition described above in an amount equivalent to 100 mg pure PS. The parents of children in both groups were asked to provide the usual meals during the study period.

PSYCHOLOGICAL EXAMINATION

Method of examination

The following items were investigated in the children at the beginning and at the end of study.

(1)Based on the AD/HD diagnostic criteria of DSM-IV (Table 2), inattention and hyperactivity & impulsiveness were assessed in scores. The assessment was made through an interview with the parents of children. The questions were answered either by "yes" or "no". "Yes" answer was scored as 1 point while "no" answer was scored as 0 point (2).

The field of disorder (Table 2) was checked in the 9 children diagnosed to have LD, and their LD was assessed in scores. The assessment was made through an interview with the parents of children. The questions were answered either by "yes" or "no". "Yes" answer was scored as 1 point while "no" answer was scored as 0 point. (3) According to the test prepared with reference to the development test of visual perception (DTVP; original version developed by Frostig et al. (18)), the visual perception task employed in the DHA intervention test was used (19). First, the tester indicated the figure to look for. Practice to check the extraction of target stimulation was performed in advance. After it was confirmed that the children have understood the task, the trial was started. A table (8 x 10) was shown to the children and they were asked to find as many figures as possible among the 80 figures that included several identical figures within 30 seconds. With an interval of 15 seconds, this task was repeated 3 times (total 90 seconds), and an average score was calculated. As no statistically significant differences were detected. a repetition effect could be excluded.

Concerning the visual and auditory short-term memory, 7 numerals from 0 to 9 were shown to the children for 10 seconds and then the same 7 numerals were read to them. Then, the children were asked to recall and write down these numerals in another piece of paper (20). When the order (position) of numerals was correct, the answer was handled as correct. According to Hirayama et al.(19), average correct answer among AD/HD children was 2.5 - 3.5 points for visual short-term memory, and 2 points for auditory short-term memory. The mean numbers of correct answers made by 4-year old and 10 ˜ 12 year old normal children are reported to be 3 and 6 respectively (21). Continuous performance test (CPT). CPT is a test developed by the group of Rosvold (22) to objectively assess the persistent concentration. According to this test, one of the numerals from 1 to 9 was randomly shown on the computer screen. The children were instructed to press the button only when "9" was shown after "1". The stimulation interval between the warning stimulation "1" and the subsequent numeral was set at 800 ms, 1500 ms or 3000 ms, and the interval was randomly changed. As to the types of wrong response, the following 2 types to investigate the inattention and impulsiveness were selected among those classified in the conventional researches using CPT. Repetition effect of CPT is denied in Yamada et al.(23).

- "9 only error"; Wrong response to target stimulation without specific warning stimulation immediately before (inattention).
- "1 only error", Wrong response to specific warning stimulation itself (impulsiveness).

All these tests were given by the same tester (specialist clinically skilled and well-versed in the development such as AD/HD, AS, LD).

(1) AD/HD (DSM-IV, 1994) (24)

1) **Attention**

Many careless mistakes Cannot remain attentive Dislikes effort Does not listen

Cannot follow the instruction Forgets activity Cannot arrange the matters in order

Lose items Becomes distracted

2) **Hyperactivity**

Nervous & fidgety Standing and walking Running around (climbing high)

Cannot play quietly Restless Talks too much

3) **Impulsiveness**

Abrupt answer Cannot wait for one's turn

Intervenes and gets in the way of conversation and game

(2) **LD**

Hearing Speaking Reading Writing Calculation Inference

Table 2. AD/HD and LD checklist

Statistic processing

The data are shown as mean values. Paired Student's t-test was applied to assess treatment effects as significant differences between 'pre' and 'post'. Accordingly, $p<0.05$ or less was considered as a significant difference while $p<0.10$ was regarded as a tendency towards significance.

RESULTS

Table 3 is summarizing the results of the study. AD/HD score was significantly improved ($p<0.01$), and the inattention component of AD/HD as well as hyperactivity & impulsiveness were also significantly improved ($p<0.01$ and $p<0.05$ respectively). No significant difference was observed with regard to the visual and auditory short-term memory.
The mean number of correct answers to visual perception task was also significantly improved ($p<0.001$). Concerning CPT, no statistic difference was observed in "1 only error" but a tendency of significance was noted in "9 only error" ($p<0.10$). The post study test was rejected by 1 child while 3 other children became incompatible with the testing procedure. It was difficult for the those 3 children to understand the task and they were unable to perform it according to the instruction. Thus, they were judged incompatible to the test. Excluding these 4 children, the results obtained from 11 children were statistically processed. Concerning the 9 children diagnosed to have LD by the attending physicians (psychiatrists), a tendency of significance was observed in the LD improvement ($p<0.10$) (Table 3).
The same results were obtained when the 2 children who had been under treatment with Ritalin® were excluded.

		AD/HD				
		Pre-study		Post-study		Intra-group difference
		M	SD	M	SD	p-value
AD/HD (n=15)						
	AD/HD score	9,93	4,96	7,93	4,91	< 0.01
	AD score	5,80	3,00	4,53	2,64	< 0.01
	HD score	4,13	2,77	3,40	2,72	< 0.05
LD (n=9)						
	Number of LD fields	4,33	1,32	3,33	1,87	< 0.1
Visual perception (n=15)						
	Number of correct answers	9,80	3,65	13,38	3,39	< 0.001
Short-term memory (n=15)						
	Visual (number of memorized numerals)	3,27	1,49	3,67	1,91	n.s.
	Auditory (number of memorized numerals)	1,73	0,96	1,80	1,08	n.s.
CPT (n=11)						
Number of errors	9 only	8,64	10,25	4,27	7,89	< 0.1
	1 only	5,27	10,56	4,73	11,49	n.s.

Table 3. Mean pre- and post-study scores

DISCUSSION

This study clearly shows that a supplementation with phosphatidylserine might improve AD/HD symptoms in children. Though there is no officially acknowledged report on an intervention study in AD/HD, PS was clinically confirmed to have extensive effects on the cerebral function (16). In this regard, it should be mentioned that phosphatidylserine (PS) is present in the brain at a much higher concentration than in other organs. It is an important component of cell membrane in the synapse of nerve cells and is deeply involved in the loculation that leads to the production and release of neurotransmitters and the activities mediated by the receptors in specific synaptic cleft. PS was shown to activate the brain, when taken as a supplement (25). PS facilitates synaptic connectivity parts, and especially improves dopamine transmission. In other words, it is beneficial for the production and release of dopamine as well as the excitation of receptors in the posterior synapse (26). A similar view was presented by Blokland et al. (27) and Crook et al. (28). PS is reported to play an important role in the maintenance of intracellular environment, neurotransmission, release from loculi, and communication between the cells. It is also an important component of cell membrane in the adjustment of cell growth. In general, PS is suggested to stimulate the dopaminergic system in the hypothalamus (29, 29), and to stimulate dopamine-sensitive adenylate cyclase (30). It is also reported that PS increases acetylcholine, noradrenalin, serotonin and dopamine in animal models and patients with Alzheimer disease (12-14, 31-35). These reports indicate that PS is involved in the regeneration of cell membrane and adjustment of neurotransmitters (mainly dopamine) in synaptic cleft.

Thus, it is useful in the reconstruction of nerve network whose function has been disturbed. It is well known that central stimulants such as methylphenidate hydrochloride are effective in AD/HD. The major action mechanism of central stimulants may be described as the activation of noradrenalin system in the brain (36) that adjusts higher cerebral function including attentiveness by freeing (releasing) noradrenalin from the sympathetic nerve terminal and chrome-affinitive cells (37, 38). There is a research that reports on the relation of not only noradrenalin but also dopamine to central stimulants. By interfering with the reuptake of these neurotransmitters from the synaptic cleft, stimulants effectively increase the respective signal intensity and duration (39-41). Huijbregts et al. (42) pointed out that intensive research based on the hypothesis of dopamine insufficiency in AD/HD is in progress at present. The improvement of AD/HD symptoms in the present trial might suggest that a PS administration is therapeutically effective in increasing the dopamine or noradrenalin concentration in the synaptic cleft even though the mechanism of inhibiting the re-uptake seemed different from that of central stimulants. The great improvement in visual perception (figure background perception) is considered to be attributable to the improved concentration in AD/HD children. The objectivity of DSM-IV is slightly insufficient because it is a non-quantitative test. However, the result of visual perception test this time objectively supported the improvement in inattentiveness indicated by DSM-IV. The "9 only error" in CPT is grasped as a carelessness problem because of the lack of response preparation to the warning stimulation "1", consequently overlooking the warning stimulation "1". Though the result remained as a tendency of significance, improvement was observed in the number of "9 only errors".

However, regarding the investigation of the carelessness, the effect remained at a level of 10 percent in the case of "9 only errors" even though the effect was observed at the 1percent level in the AD score of DSM-IV check list and at the 0.1percent level in the visual perception task. The "1 only error" occurs as a wrong response caused by reacting to the warning stimulation "1" itself without waiting for the target stimulation "9". Therefore, the error can be grasped as a problem of inhibition, especially that of impulsiveness. A slight decrease in the mean value (from 5.27 to 4.73) was observed in "1 only error" in this experiment, though it did not reach significance. Considering that the effect was observed at the 5percent level in the HD score in the DMS-IV check list, it was possible to interpret that the "1 only error" focuses on the impulsiveness rather than hyperactivity regarding the hyperactivity & impulsiveness of AD/HD and that the content of DSM-IV is different from that of CPT in that the judgment is based on the wrong response to a sign (numeral) in CPT while the judgment is based on the daily life scenes in DSM-IV, etc.

A difference in the significant level between the check list and CPT was similarly observed in the above mentioned carelessness. In this regard, further research should be made on the reliability of CPT itself and the validity of test. According to the DSM-IV check list, the hyperactivity and impulsiveness was significantly improved but the extent of improvement was slightly inferior to that observed in the carelessness. According to the CPT task, there was no significant difference even though a tendency of significance was noted in carelessness and a tendency of decrease was noted in impulsiveness. Considering these results, PS seems to be more effective against carelessness rather than against hyperactivity and impulsiveness. However, carelessness may serve as a cause of hyperactivity & impulsiveness. Therefore, it is assumed that PS can also improve "1 only error" in CPT, that is, impulsiveness, if the conditions including the PS administration period and dosing regimen are optimally adapted. Zanotti et al. (43) orally administered PS at 50 mg/kg/day for 12 weeks to aged (cognitive) impaired rats and reported on the improvement of spatial memory (place-navigation deficit). Based on the results of research, we expected to improve the memory of patients with AD/HD by the treatment with PS, and conducted a short-term memory test. However, the result did not meet the expectation even though the reason why is not clear. In this regard, Nilsson et al. (44) conducted an experiment in rats and reported that severe and persistent place-navigation deficit was influenced by a combined cholinergic-serotonergic impairment. The cause and mechanism of memory disorder in AD/HD may be different from those in cerebral disorder rat.

Concerning the LD symptoms that are often superposed with AD/HD, some improvement (tendency of significance) was observed in the degree of LD. Since the number of children with LD diagnosed by their attending physicians was small (9 among the 15 subjects of this study), re-investigation in the future is desirable by increasing the number of samples. Considering the negative effects of LD, especially those on learning at school, the benefits of an PS administration are expected to be even more impressive if PS could be shown to improve not only AD/HD but also LD. The present study was started in 21 children, 15 of which completed the study and 6 dropped out. It was not possible to obtain the cooperation of family in 2 of these drop-out cases (the informed consent was acquired from both mothers but the understanding of father was not obtained for 1 of the 2 children and that of grandmother for the other). According to the questionnaire survey conducted after the intervention test, 1 child specified regurgitation of unpleasant fluid after the intake of supplement while 3 children answered that the size of capsule was too large and that it was difficult to swallow it. 3 other children felt uncomfortable as if they were taking a medicine (plural number of answers). All these demerits are expected to have served as the causes of drop-out. Many of the children who completed the test also indicated that it might have been easier to take the supplement if the capsule size had been smaller. Despite this demerit, as many as 15 of 21 children completed the test. This ratio is impressive for an AD/HD study, even keeping in mind the relative short duration of the study (2 months).

According to the double blind clinical study by Hirayama et al. (45), 3.6 g/week of DHA (docosahexaenoic acid) mixed in food and drinks was given to AD/HD children for 2 months but rather than improving AD/HD symptoms, the treatment even let to a slight deterioration the symptoms. However, the "explosion" (impulsive aggression) that often occurs as the secondary problem was significantly improved. This aggression is considered as one of the defensive reactions to interpersonal anxiety. With reference to the research made by Hamazaki et al. (45, 46) on the relation of DHA to aggression, the impulsiveness is induced by the decrease in serotonin. That means, the improvement in aggression is assumed to be the effect of serotonin increase by DHA (47). Thus, a supplement that combines PS and DHA might demonstrate a synergistic therapeutic effect in the AD/HD symptoms including anxiety tendency and tendency of impulsive aggression and resistance. Further research is expected to confirm the significant beneficial effects of PS on AD/HD and to expand its application.

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