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CONTENTS

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Dietary Variety Contributes to Weight Gain in the Outpatient Treatment of Anorexia Nervosa

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Abstract

Background

Anorexia nervosa is an eating disorder characterized by severe underweight, and thus, weight gain is the primary treatment goal. Patients with anorexia nervosa often consume a diet that lacks variety and is biased toward certain foods. However, few studies have examined the association between dietary variety and anorexia nervosa prognosis. Quality of life, which is related to dietary patterns, is an important indicator of recovery from anorexia nervosa. This study aimed to determine the relationship among dietary variety, quality of life, and weight gain during outpatient treatment in anorexia nervosa.

Methods

A total of 44 female anorexia nervosa patients with a body mass index (BMI) of <17 kg/m^2 and who were treated as outpatients were included. The patients recorded food images for 7 consecutive days using a smartphone application. Data on age, height, weight, anorexia nervosa subtype (restricting type, binge-eating/purging type), and quality of life scores were collected. Dietary variety scores were assessed from dietary images, and multiple regression analysis was performed for the overall anorexia nervosa and anorexia nervosa subtypes to examine the factors associated with increased BMI at 6 months.

Results

The dietary variety score was significantly associated with an increased BMI in the overall patients. This significant association was observed in the anorexia nervosa restricting subgroup but not in the anorexia nervosa binge-eating/purging subgroup.

Conclusions

Greater dietary variety significantly contributes to weight gain in patients with anorexia nervosa. Thus, incorporating dietary variety into outpatient dietary guidance may enhance recovery outcomes in patients with anorexia nervosa.

Key Words: Anorexia nervosa; Dietary variety; Quality of life; Weight gain; Outpatient treatment

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Introduction

Eating disorders (EDs) are psychiatric conditions characterized by abnormal eating behaviors and patterns, including anorexia, overeating, strong desire to lose weight, fear of obesity, obsession with weight and body shape, and an excessive impact on self-esteem. Anorexia nervosa (AN), the most common type of ED, is characterized by significantly low body weight and can be classified into two types[1]. In the restricting eating type (AN-R), weight loss is primarily due to reduced food intake or excessive exercise. In the binge-eating/purging type (AN-BP), episodes of overeating are followed by compensatory behaviors such as self-induced vomiting or the abuse of laxatives or diuretics to prevent weight gain, in addition to weight loss. Patients often resist eating because of fear of weight gain or obesity and consume small amounts of food. When they do eat, they typically follow unusual eating patterns, such as avoiding carbohydrates and fats, and eating only foods they perceive as safe, leading to very selective eating[2]. In addition, their preoccupation with how they eat often limits their overall lifestyle by restricting where, when, and how they eat. This leads to social and familial isolation[3,4] and a decline in quality of life (QOL)[5]. Bizarre eating styles often become habitual, prolonging disease duration[6,7].

Patients with AN often lack awareness about the severity of their physical abnormalities, and a high mortality rate has been reported[8]. Weight is an important prognostic factor in AN, and weight gain is the primary therapeutic goal of treatment[9]. Outpatient treatment includes psychotherapy for psychological problems related to the cause of ED, as well as dietary and lifestyle guidance, with the goal of weight gain and restoration of appropriate eating patterns[9,10]. Dietary guidance for patients with EDs includes advising them on the caloric intake necessary to maintain or gain weight and educating them about the composition of a nutritionally balanced diet and appropriate eating habits. As it is important in nutritional guidance to understand a patient's daily eating pattern, self-monitoring using a form to record the foods consumed by the patient is commonly used[11].

Recently, the use of smartphone application (app) to record more detailed dietary information has been reported[12,13]. Nutritional guidance emphasizes eating three meals per day (or sometimes more frequent meals to promote weight gain) and maintaining a diet with various nutrients[2]. However, the content of the guidance is often based on the clinician's rules of thumb and generalizations, and studies investigating its impact on prognosis and weight gain are limited[14-16]. Additionally, one aim of lifestyle guidance is to improve the QOL. Many reports have suggested a diverse range of interactive effects between QOL and AN symptoms (e.g., ED pathology, eating behaviors, eating styles, and weight changes)[5,17-20]. QOL is important for assessing recovery from AN. It is also considered to be associated with dietary style, including variety, and to influence weight gain.

This study aimed to investigate whether dietary variety was beneficial for the outpatient treatment of AN.

Methods

Study design and patients

This was a retrospective cohort study based on data entered into medical records and a smartphone app used to record dietary habits. AN patients who visited the outpatient department of neuropsychiatry at Osaka Metropolitan University Hospital (formerly Osaka City University Hospital) between January 1, 2021, and December 31, 2022 were included. Patients who received inpatient treatment during the study period were excluded. The patients had a body mass index

(BMI) of less than 17 kg/m^2, which corresponds to moderate or more severe AN according to the DSM-5 severity criteria, and recorded dietary images on the app for at least 7 consecutive days during outpatient treatment. AN was diagnosed by a psychiatrist with an outpatient practice specializing in EDs following the Diagnostic and Statistical Manual of Mental Disorders, 5th edition. The observation period for weight gain was 6 months after the start of recording using the app. The app was developed for research purposes and named "Chant"; it was downloaded free of charge from Google Play and the Apple App Store, and only the subjects in this study were able to log in and use the app.

Procedure

7-Day Dietary Variety Score

The patients took images of their meals immediately prior to eating for at least 7 days. After the meal, they also entered the name of the food, presence and frequency of eating behavior abnormalities such as overeating and vomiting, feelings of mood, and environment (where and with whom) in which the food was consumed. The 7-day Dietary Variety Score (DVS7) was defined as the "number of types" of food consumed divided by the "cumulative number" of foods consumed. Particularly, the same food consumed multiple times was counted only once in the "number of types" of food, while the number of times it was consumed was counted in the "cumulative number" of foods consumed. Foods prepared in distinctly different ways (e.g., baked potatoes, mashed potatoes, and French fries) were counted as separate items. Combination foods (e.g., pizza) were counted as a single unit and were not broken down into components (e.g., pizza crust, cheese, and tomato sauce). Beverages (e.g., water and juice) and condiments (e.g., salt, pepper, spices, herbs, ketchup, and mustard) were not counted. Dietary records and DVS7 counts were reviewed by a psychiatrist with an outpatient practice specializing in EDs.

World Health Organization Quality of Life Measure Brief

QOL was assessed using the World Health Organization Quality of Life Measure Brief (WHOQOL-BREF) developed by the World Health Organization (WHO). The reliability and validity of the WHOQOL-BREF have been established previously. Briefly, the tool consists of 26 questions in 4 areas (1: physical health (7 questions), 2: psychological health (6 questions), 3: social relationships (3 questions), and 4: environmental health (8 questions)) and general QOL section (2 questions). Each item is rated on a 5-point Likert scale from 1 to 5. The QOL mean, which indicates overall QOL, is calculated from the total score of all items, with higher scores indicating a higher overall QOL.

BMI increase

BMI increase was defined as the difference in BMI (calculated as the weight in kilograms divided by the height in meters squared) at the start of app use and 6 months later.

Statistical analysis

Patient characteristics for the overall AN group and by AN subgroup at the beginning of the study are presented using descriptive statistics, means, and standard deviations (SDs). Continuous variables were compared between the subgroups using Student's t-test. Correlations between each measure were calculated to assess the association between DVS7 and QOL. Multiple regression analysis was used to examine the factors influencing the rate of BMI increase in the overall group and by AN subgroup. The independent variables included age at study enrollment, BMI, DVS7, QOL mean, and AN subtype, which were entered using the forced entry method. In this study, the

significant level was set at 5%. All statistical analyses were performed using SPSS 29.0 for Mac OS X (SPSS Japan, Tokyo, Japan).

Ethical statement

The study protocol was reviewed and approved by the Ethics Committee of Osaka Metropolitan University (authorization number: 2020-156). The need for informed consent was waived owing to the retrospective study design and use of de-identified data.

Results

44 patients were included in the study, 30 (68.2%) patients had AN-R, and 14 (31.8%) patients had AN-BP. All patients were female. Table 1 presents the patient characteristics. There were no significant differences between the subgroups with respect to age or disease duration at baseline. Baseline BMI was significantly higher in the AN-BP subgroup than in the AN-R subgroup (15.24±

Table 1. Patient characteristics

Characteristic	Total (n=44)	AN-R subgroup (n=30)	AN-BP subgroup (n=14)	p Value
Age (years)[a]	24.87±10.42	23.32±10.59	28.20±9.58	0.153
Disease duration (years)[a]	4.81±7.27	3.38±5.19	7.86±10.00	0.056
Baseline BMI (kg/m^2)[a]	14.60±1.45	14.31±1.30	15.24±1.58	0.046*
BMI after 6 months (kg/m^2)	16.06±2.50	15.56±2.32	17.12±2.63	0.054
BMI increase (kg/m^2)	1.45±2.56	1.26±2.49	1.88±2.74	0.458
DVS7	0.45±0.13	0.42±0.14	0.49±0.11	0.106
QOL-Physical health[b]	2.94±0.78	3.09±0.73	2.63±0.82	0.070
QOL-Psychological health[b]	2.47±0.93	2.66±0.88	2.04±0.92	0.035*
QOL-Social relationships[b]	3.06±0.77	2.03±0.70	2.88±0.90	0.298
QOL-Environmental health[b]	3.35±0.81	3.57±0.75	2.88±0.74	0.006*
QOL-General[b]	2.49±0.92	2.70±0.89	2.04±0.87	0.025*
QOL-mean[b]	2.94±0.75	3.12±0.70	2.55±0.72	0.017*

a: at start of study; b: at initial follow-up. * $p<0.05$.

Categorical variables are reported as numbers (percentages). Continuous variables are reported as means±SDs and compared using Student's t-test.

AN-R, anorexia nervosa restricting type; AN-BP, anorexia nervosa binge-eating/purging type; BMI, body mass index (kg/m^2); DVS7, 7-day Dietary Variety Score; QOL, quality of life. Each QOL item is assessed using the World Health Organization Quality of Life Measure Brief Version (WHOQOL-BREF).

Table 2. Correlations between DVS7 and each of the QOL area for the overall AN group and AN subgroups

	Correlation Coefficients (r)					
	QOL-Physical health	QOL-Psychological health	QOL-Social relationships	QOL-Environmental health	QOL-General	QOL-mean
DVS7 in the overall AN group (n=44)	−0.144	−0.191	−0.077	−0.140	−0.380*	−0.188
DVS7 in AN-R subgroup (n=30)	−0.017	−0.046	0.119	−0.092	−0.308	−0.065
DVS7 in AN-BP subgroup (n=14)	−0.252	−0.339	−0.401	0.092	−0.383	−0.243

* $p<0.05$.

DVS7, 7-day Dietary Variety Score; AN, anorexia nervosa; AN-R, anorexia nervosa restricting type; AN-BP, anorexia nervosa binge-eating/purging type; and QOL, quality of life. Each QOL item is assessed using the World Health Organization Quality of Life Measure Brief Version (WHOQOL-BREF).

1.58 kg/m^2 vs 14.31±1.30 kg/m^2, $p<0.05$). There were no significant between-subgroup differences in BMI after 6 months or in BMI increase at 6 months. DVS7 was also not significantly different between the AN-R subgroup and AN-BP subgroup (0.42±0.13 vs 0.49±0.10, $p<0.05$). The QOL mean was significantly higher in the AN-R subgroup than in the AN-BP subgroup (3.12±0.70 vs 2.55±0.72,

Table 3-1. Multiple regression analysis of the effects of age, AN subtype, baseline BMI, DVS7, and QOL-mean on BMI increase in the overall AN group

Factor	B	SE	β	t Value	p Value
Age at study entry	−0.081	0.037	−0.330	−2.170	0.036*
AN subtype	1.046	0.856	0.193	1.223	0.229
Baseline BMI	−0.774	0.267	−0.438	−2.899	0.006*
DVS7	6.703	2.648	0.348	2.532	0.016*
QOL-mean	−0.398	0.514	−0.116	−0.774	0.444

$R^2=0.352$, adjusted $R^2=0.267$, $F=4.137$, $p<0.01$.

Age, AN subtype, baseline BMI, DVS7, and QOL mean are entered as independent variables using the forced entry method. AN subtypes, which are nominal scale variables, are set as dummy variables. n=44. *$p<0.05$.

B, unstandardized coefficient; SE, standard error; β, standardized partial regression coefficient; AN, anorexia nervosa; BMI, body mass index (kg/m^2); DVS7, 7-day Dietary Variety Score; and QOL mean, mean of the quality of life assessed using the World Health Organization Quality of Life Measure Brief Version (WHOQOL-BREF).

Table 3-2. Multiple regression analysis of the effects of age, baseline BMI, DVS7, and QOL mean on BMI increase in the AN-R subgroup

Factor	B	SE	β	t Value	p Value
Age at study entry	−0.048	0.044	−0.205	−1.091	0.286
Baseline BMI	−0.676	0.350	−0.354	−1.932	0.065
DVS7	7.922	2.905	0.443	2.727	0.012*
QOL-mean	−0.475	0.593	−0.133	−0.801	0.431

$R^2=0.406$, adjusted $R^2=0.311$, $F=4.272$, $p<0.01$. Age, baseline BMI, DVS7, and QOL-mean are entered as independent variables using the forced entry method. n=30. *$p<0.05$.

B, unstandardized coefficient; SE, standard error; β, standardized partial regression coefficient; AN-R, anorexia nervosa restricting type; BMI, body mass index (kg/m^2); DVS7, 7-day Dietary Variety Score; and QOL mean, mean of the quality of life assessed using the World Health Organization Quality of Life Measure Brief Version (WHOQOL-BREF).

Table 3-3. Multiple regression analysis of the effects of age, baseline BMI, DVS7, and QOL mean on BMI increase in the AN-BP subgroup

Factor	B	SE	β	t Value	p Value
Age	−0.153	0.092	−0.534	−1.668	0.130
Baseline BMI	−0.785	0.486	−0.453	−1.617	0.140
DVS7	6.817	7.884	0.266	0.865	0.410
QOL-mean	−0.206	1.098	−0.054	−0.187	0.856

$R^2=0.336$, adjusted $R^2=0.042$, $F=1.141$, $p=0.40$. Age, baseline BMI, DVS7, and QOL-mean are entered as independent variables using the forced entry method. n=14.

B, unstandardized coefficient; SE, standard error; β, standardized partial regression coefficient; AN-BP, anorexia nervosa binge-eating/purging type; BMI, body mass index (kg/m^2); DVS7, 7-day Dietary Variety Score; and QOL mean, mean of the quality of life assessed using the World Health Organization Quality of Life Measure Brief Version (WHOQOL-BREF).

$p<0.05$). With respect to QOL areas and general QOL, the AN-R subgroup scored significantly higher in psychological health, environmental health, and general QOL than did the AN-BP subgroup.

Table 2 presents the correlation between DVS7 and each QOL area for the overall AN group and AN subgroups. No correlations were found between DVS7 and QOL areas (physical health, psychological health, social relationships, environmental health, general QOL, and QOL mean). Only a negative correlation ($p<0.05$) was observed with general QOL. Similar results were found in the AN-R and AN-BP subgroups; however, there were also no significant correlations between DVS7 and any of the QOL areas.

Table 3-1 presents the effects of age at study entry, BMI, DVS7, QOL mean, and AN subtype on the BMI increase in the overall AN group. Lower age, lower BMI at study enrollment, and higher DVS7 scores were significantly associated with increased BMI. No significant relationship was found between AN subtype and QOL. Table 3-2 presents the effects of age at baseline, BMI, DVS7, and QOL mean on BMI increase in the AN-R subgroup. Among the independent variables, only a high DVS7 score was significantly associated with an increase in BMI. Table 3-3 presents the effects of age at study entry, BMI, DVS7, and QOL mean on BMI increase in the AN-BP subgroup. No independent variable was significantly associated with an increase in BMI.

Discussion

This study determined the relationship among dietary variety, QOL, and weight gain in patients with AN undergoing outpatient treatment. The results showed that a BMI increase 6 months after study entry was significantly associated with a higher DVS7 in the overall AN group and in the AN-R subgroup, indicating that a greater variety of usual food intake is associated with a greater degree of weight gain. Lower age and baseline BMI were also predictors of a greater increase in BMI in the overall AN group. These findings provide evidence for nutritional guidance to enhance the prognosis of AN.

Many patients with EDs avoid foods with specific ingredients or foods in specific categories[2], resulting in a lack of variety in the foods consumed. These patients also tend to have limited interactions with others (often through eating and drinking) and experience social isolation[3,4]. Furthermore, limited access to a variety of food choices may lead to difficulty in consuming adequate calories in the long term[16] and may cause ED persistence. In addition to increasing food intake, increasing food variety with the aim of improving nutrient imbalances (micronutrient deficiencies are common[21]) has been recommended in the dietary guidance for the outpatient care of AN based on existing evidence[22,23]. Our finding that the magnitude of food variety influences weight gain in patients with AN is valuable as it provides evidence that dietary advice should emphasize the consumption of a wide variety of foods.

The findings are consistent with those reported previously. Vanzhula et al reported that the degree of dietary variety was associated with food insecurity (anxiety about eating a variety of foods) and confidence in appropriate dietary behavior (normative dietary behavior self-efficacy) in AN patients who participated in an inpatient program[14]. The therapeutic significance of greater dietary variety was also described. Schebendach et al also suggested that greater food variety is associated with fewer relapses in the domains of eating behavior, physiology, relationships with the opposite sex, psychological status, family relationships, and overall life status (including academic and employment status) among weight regainers with AN, thus also affecting prognosis[15]. These results support the

recommendation to encourage greater food variety in the treatment of patients with AN.

The definition and measurement of dietary variety can vary across studies[24]. In this study, we observed that AN patients often restrict their diet to foods perceived as safe. We defined limited dietary variety as consistently eating only a narrow range of foods, while greater dietary variety involved broader food choices. To quantify dietary variety, we developed the DVS7 score, which reflects the "number of types" of foods consumed relative to the "cumulative number" of foods, providing a more nuanced measure than a simple food count.

As to be noted, this study achieved relatively good average weight gain. Various apps are being developed for ED treatment[13], although their impact on weight gain remains uncertain. Some studies suggest that apps may help improve ED symptoms and reduce social isolation[25,26]. In this study, app usage may have positively influenced patients' motivation and contributed to weight gain. Even for chronic patients, beginning to manage eating habits using this app may have encouraged beneficial eating behavior changes.

Our analyses by AN subtype showed results similar to those for the overall AN group, with greater food variety in the AN-R subgroup contributing to weight gain. Patients with AN-R are generally described as constrained and obsessional[27]. As such, they are more likely to exercise stricter control over their diet. Particularly, patients with AN-R are resistant to behavioral changes that increase variety; however, those who are able to make these changes may have better treatment outcomes and gain more weight. However, the present study did not find a significant relationship between dietary variety and weight gain in AN-BP. One reason for this may be that overeating was included in the daily dietary records of the AN-BP subgroup, which may have influenced the results. Given that the DVS7 used in this study also counted the types of foods that the patients themselves rated as worthy of overeating, it is possible that overeating may have increased food variety. Consuming a variety of foods through overeating is not a therapeutic behavior, cannot be evaluated as an appropriate eating behavior for recovery, and may not have a positive impact on weight gain.

Several studies have reported that QOL influenced the course of EDs. Milic et al observed that a low QOL could maintain unhealthy eating patterns[17]. QOL impairment is associated with a lower BMI in AN-BP[5]. Conversely, positive changes in eating behavior have a direct positive impact on QOL[17]. Mitchison et al reported that improved QOL may be associated with behavioral changes and weight gain[18]. Particularly, QOL is an important therapeutic parameter related to ED symptoms, weight change, and eating patterns. In the current study, patients with a higher DVS7 in the overall AN group had a significantly lower general QOL on the WHOQOL-BREF, but no correlations were found in other QOL areas, including the QOL mean. There was also no correlation between the DVS7 and QOL in the AN-R and AN-BP subgroups. Furthermore, the QOL mean did not affect the BMI increase at 6 months after study entry. Although greater dietary variety is an important goal during outpatient visits in patients with AN, this effort often involves difficulty and pain; therefore, greater food variety may not have led to a higher self-rated QOL in this study. In addition, QOL did not affect BMI increase in any analysis. These results may have been due to the small sample size and should be verified in future studies with larger sample sizes.

In the analysis of the overall AN group, patients' younger age made them more likely to gain weight. Our results are in line with those reported by Wild et al that younger patients or those with shorter disease durations were more likely to recover from the disease[28]. Additionally, in the evaluation of the overall AN group, the lower the BMI, the greater the weight gain. This result is in

contrast to previous findings of a higher baseline BMI being associated with a better outcome in studies that evaluated AN outcomes with respect to recurrence and BMI trends over a period of 9 to 15 months[28-30]. The difference may be because this study focused on the increase in BMI over a short period. This result was not surprising, as participants with a lower BMI have a higher opportunity for an increase in BMI.

This study has some limitations. First, patients who used the dietary record app for outpatient treatment were evaluated, and this may have introduced bias owing to high motivation for treatment. Second, the dietary data were based on self-records, and this had limitations in accuracy. Third, the timing of when the participants started using the app was not consistent. In the early stages of the illness, weight may fluctuate more easily compared to the chronic phase, and differences in the timing of app usage may have affected the results. Fourth, it is possible that improvements in nutritional balance were a factor in weight gain, however, the dietary amount or its nutritional content were not examined in this study. Finally, the study period was only 6 months. A longer follow-up period may be necessary to validate the impact of dietary variety on the prognosis of AN. Further, a larger sample size may reveal relationships not detected in the present study.

In conclusion, greater dietary variety is associated with weight gain in AN, especially in AN-R patients. This study is original and valuable in providing evidence for the clinical rule of thumb that incorporating dietary variety into dietary guidance for AN outpatients enhance the recovery outcomes.

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All authors have no COI to declare regarding the present study.

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References

1. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 5th ed. Washington DC: American Psychiatric Association, 2013.
2. David M. Garner, Paul E. Garfinkel. Handbook of Treatment for Eating Disorders: 2nd Edition. New York: The Guilford Press, 1997.
3. Cardi V, Mallorqui-Bague N, Albano G, et al. Social difficulties as risk and maintaining factors in anorexia nervosa: a mixed-method investigation. Front Psychiatry 2018;9:12.
4. Makri E, Michopoulos I, Gonidakis F. Investigation of loneliness and social support in patients with eating disorders: a case-control study. Psychiatry International 2022;3:142-157.
5. DeJong H, Oldershaw A, Sternheim L, et al. Quality of life in anorexia nervosa, bulimia nervosa and eating disorder not-otherwise-specified. J Eat Disord 2013;1:43.
6. Uniacke B, Timothy Walsh B, Foerde K, et al. The role of habits in anorexia nervosa: where we are and where to go from here? Curr Psychiatry Rep 2018;20:61.
7. Sysko R, Walsh BT, Schebendach J, et al. Eating behavior among women with anorexia nervosa. Am J Clin Nutr 2005;82:296-301.
8. Berkman ND, Lohr KN, Bulik CM. Outcomes of eating disorders: a systematic review of the literature. Int J Eat Disord 2007;40:293-309.
9. Marzola E, Nasser JA, Hashim SA, et al. Nutritional rehabilitation in anorexia nervosa: review of the literature and implications for treatment. BMC Psychiatry 2013;13:290.
10. National Guideline Alliance (UK). Eating Disorders: Recognition and Treatment. London: National Institute for Health and Care Excellence (NICE); 2017.
11. Keshen A, Helson T, Ali S, et al. Efficacy and acceptability of self-monitoring via a smartphone application versus traditional paper records in an intensive outpatient eating disorder treatment setting. Eur Eat Disord

Rev 2020;28:473-479.
12. Wasil AR, Patel R, Cho JY, et al. Smartphone apps for eating disorders: a systematic review of evidence-based content and application of user-adjusted analyses. Int J Eat Disord 2021;54:690-700.
13. O'Leary T, Torous J. Smartphone apps for eating disorders: an overview of the marketplace and research trends. Int J Eat Disord 2022;55:625-632.
14. Vanzhula I, Duck SA, Pletch A, et al. Greater dietary variety is associated with lower food anxiety at discharge from intensive eating disorder treatment. Int J Eat Disord 2023;56:1365-1377.
15. Schebendach JE, Mayer LE, Devlin MJ, et al. Dietary energy density and diet variety as predictors of outcome in anorexia nervosa. Am J Clin Nutr 2008;87:810-816.
16. Schebendach JE, Mayer LE, Devlin MJ, et al. Food choice and diet variety in weight-restored patients with anorexia nervosa. J Am Diet Assoc 2011;111:732-736.
17. Milic J, Stankic D, Stefanovic D. Eating disorder and quality of life. In: Patel VB, Preedy VR, editors. Eating Disorders. Heidelberg: Springer, 2023. pp. 353-365.
18. Mitchison D, Dawson L, Hand L, et al. Quality of life as a vulnerability and recovery factor in eating disorders: a community-based study. BMC Psychiatry 2016;16:328.
19. Padierna A, Quintana JM, Arostegui I, et al. Changes in health related quality of life among patients treated for eating disorders. Qual Life Res 2002;11:545-552.
20. Bamford B, Barras C, Sly R, et al. Eating disorder symptoms and quality of life: where should clinicians place their focus in severe and enduring anorexia nervosa? Int J Eat Disord 2015;48:133-138.
21. Hadigan CM, Anderson EJ, Miller KK, et al. Assessment of macronutrient and micronutrient intake in women with anorexia nervosa. Int J Eat Disord 2000;28:284-292.
22. McMaster CM, Franklin J, Hart M, et al. The Role of the dietitian. In Patel VB, Preedy VR, editors. Eating Disorders. Heidelberg: Springer, 2023. pp. 385-410.
23. Graves LL, Scribner C. Medical nutrition therapy for eating disorders. In: Smolak L, Levine MP, editors. The Wiley Handbook of Eating Disorders. New Jersey: John Wiley & Sons, Ltd, 2015. pp. 843-858.
24. Vadiveloo M, Dixon LB, Parekh N. Associations between dietary variety and measures of body adiposity: a systematic review of epidemiological studies. Br J Nutr 2013;109:1557-1572.
25. Neumayr C, Voderholzer U, Tregarthen J, et al. Improving aftercare with technology for anorexia nervosa after intensive inpatient treatment: a pilot randomized controlled trial with a therapist-guided smartphone app. Int J Eat Disord. 2019;52:1191-1201.
26. Holgersen G, Abdi-Dezfuli SE, Friis Darrud S, et al. Adolescents' perspectives on a novel digital treatment targeting eating disorders: a qualitative study. BMC Psychiatry 2024;24:423.
27. Curzio O, Maestro S, Rossi G, et al. Transdiagnostic vs. disorder-focused perspective in children and adolescents with eating disorders: findings from a large multisite exploratory study. Eur Psychiatry 2018;49:81-93.
28. Wild B, Friederich HC, Zipfel S, et al. Predictors of outcomes in outpatients with anorexia nervosa - Results from the ANTOP study. Psychiatry Res 2016;244:45-50.
29. Castro-Fornieles J, Casulà V, Saura B, et al. Predictors of weight maintenance after hospital discharge in adolescent anorexia nervosa. Int J Eat Disord 2007;40:129-135.
30. Bean P, Loomis CC, Timmel P, et al. Outcome variables for anorexic males and females one year after discharge from residential treatment. J Addict Dis 2004;23:83-94.

Osaka City Med. J. Vol. 71, 61-71, 2025

Subthreshold Hypomanic Symptoms and Sensory Processing Disorder in Pediatric Clinical Populations: Prevalence and Association with Severity

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Abstract

Background

Subthreshold hypomanic symptoms are strong predictors of psychiatric disorder onset and suicidal ideation. Although sensory processing disorder has been associated with subthreshold hypomanic symptoms in adults, no study has examined this relationship in children and adolescents. This study aimed to evaluate the prevalence and severity of sensory processing disorder in children and adolescents with subthreshold hypomanic symptoms and to clarify their relationship.

Methods

We included who visited our institution between April 2018 and April 2023. The prevalence and severity of sensory processing disorder were also assessed. Subthreshold hypomanic symptoms were identified based on the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition criteria, and sensory processing disorder was evaluated using the Japanese version of the Short Sensory Profile.

Results

The particpants were categorized into those with subthreshold hypomanic symptoms (n=32, 11.4%) and those without such symptoms (n=249, 88.6%). The prevalence of sensory processing disorder and its severity were significantly higher in the subthreshold hypomanic group (43.8%) than in the clinical control group (12.0%). Even after adjusting for confounding factors, such as age, sex, internalizing and externalizing problems, low income, and neurodevelopmental disorder traits, subthreshold hypomanic symptoms remained significantly associated with sensory processing disorder severity.

Conclusions

This study suggests that children and adolescents with subthreshold hypomanic symptoms have a higher frequency and severity of sensory processing disorder. Comprehensive support, including

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sensory processing disorder assessment, may help prevent future psychiatric disturbances in children with subthreshold hypomanic symptoms for whom there are currently no effective intervention methods.

Key Words: Subthreshold hypomania; Sensory processing; Bipolar disorder; Buicide; Children

Introduction

Subthreshold hypomanic symptoms are subsyndromal manifestations of the manic state associated with bipolar disorder[1]. These symptoms, such as mood elevation, irritability, grandiosity, decreased need for sleep, distractibility, pressured speech, and increased goal-directed behavior, do not meet the full criteria for mania but significantly impact individuals[1]. Recent research has highlighted that these symptoms increase the risk of developing bipolar disorder by up to 50 times and are strong predictors of depression, substance abuse, and suicide attempts[2-4]. The prognosis worsens with earlier onset in childhood or adolescence[5]. Despite the importance of early identification, subthreshold hypomanic symptoms in children often overlap with other conditions, complicating diagnosis[6]. Therefore, more objective and reliable assessment tools are essential[7].

Sensory processing disorder (SPD) is a condition in which the brain has difficulty receiving, organizing, and responding to sensory information from the environment. Sensory input, such as sights, sounds, touch, and smells, can become overwhelming, underwhelming, or confusing for individuals with SPD[8]. While SPD affects 5%-13% of typically developing children[9], it is more prevalent in clinical populations, especially among those with neurodevelopmental and psychiatric disorders. Previous studies have demonstrated associations between SPD and conditions such as psychotic disorders[10], mood disorders, anxiety disorders[11], and emotional dysregulation[12], but few have investigated the relationship between SPD and subthreshold hypomanic symptoms in children. Recent studies in adult psychiatry have revealed an association between subthreshold hypomanic symptoms and SPD. Patients with subthreshold hypomanic symptoms are more likely to exhibit SPD[13], and evidence suggests the presence of severe SPD in such patients[14,15]. Thus, it is plausible that children with subthreshold hypomanic symptoms may also exhibit SPD.

Therefore, this study aimed to investigate the association between the prevalence and severity of SPD and subthreshold hypomanic symptoms in a clinical pediatric population and to examine the prevalence and nature of comorbid conditions.

Methods

Participants

The study included aged 5 to 17 years who were referred to the Department of Neuropsychiatry of Osaka City University Hospital (currently Osaka Metropolitan University Hospital) between April 2018 and April 2023. Participants were required to attend the clinic for at least 3 months and were evaluated by a multidisciplinary team, including child psychiatrists, psychologists, and psychiatric social workers. Children meeting the following criteria were excluded from the study: children whose parents were chronically absent or did not consent to participate in the study, children with intellectual disabilities that made symptom evaluation difficult (IQ <70 based on the Wechsler Intelligence Scale for Children, Third or Fourth Edition), children in an acute psychotic state, children with severe neurological disorders or intractable epilepsy, and children diagnosed with

bipolar disorder. Socioeconomic status has been shown to affect brain regions associated with language, executive function, and attention and is also strongly related to health outcomes[16]. Therefore, this study conducted interviews to gather information on parental absence, family income, and duration of parental education. Households receiving public assistance or with an annual income of less than 3 million yen (approximately 20000 USD) were defined as low-income households based on 50% of the median national household income[17], following previous study[18]. Prior to participating in the study, written informed consent was obtained from all children and their guardians. The study protocol was reviewed and approved by the Ethics Committee of the Graduate School of Medicine, Osaka City University (approval number: 3527), and was conducted in accordance with the Declaration of Helsinki and its subsequent amendments.

Procedures

Assessment of subthreshold hypomanic symptoms

Subthreshold hypomanic symptoms were assessed using the diagnostic criteria for "bipolar disorder that were not otherwise specified", as outlined in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5). Semi-structured interviews were conducted with the parents to evaluate whether the children met the following criteria: a hypomanic episode lasting only 2 to 3 days (elevated mood and three or more other manic symptoms, or irritable mood and four other manic symptoms); a hypomanic episode of insufficient symptoms lasting 4 days or more (elevated mood and one or two other hypomanic symptoms, or irritable mood and two or three other manic symptoms). Children who met either of these criteria were classified into the subthreshold hypomania group.

Assessment of SPD

SPD was assessed using the standardized Japanese version of the Short Sensory Profile (SSP). The parents of the children evaluated functional behaviors related to SPD using a 38-item questionnaire covering seven domains: Tactile Sensitivity, Taste/Smell Sensitivity, Movement Sensitivity, Underresponsive/Seeks Sensation, Auditory Filtering, Low Energy/Weak, Visual/Auditory Sensitivity, and Visual/Auditory Sensitivity. The SSP utilizes a 5-point Likert scale for parents to rate behaviors in response to various sensory events[19]. The Japanese version, which includes some cultural modifications but remains largely faithful to the original, expands the age range to 3-17 years. Higher scores indicate lower adaptive functioning and greater severity of SPD. Children whose total SSP score fell within the "definite difference" range (2 standard deviations or more below the mean) were classified as having SPD, based on a prior research[20].

Assessment of general psychopathology

To evaluate a broad spectrum of psychopathology, we used the standardized Japanese version of the Child Behavior Checklist (CBCL), which was completed by the parents of the participants. The CBCL, developed by Achenbach and Dumenci, is a parent-reported measure consisting of 113 items that assess the frequency and severity of behavioral and emotional problems during childhood[21]. Each item is rated on a 3-point scale: 0=not true (as far as you know); 1=somewhat or sometimes true; 2=very true or often true. The scale provides scores in three domains (Total Problems, Internalizing Problems, and Externalizing Problems) as well as eight subscales (Withdrawn, Somatic Complaints, Anxious/Depressed, Social Problems, Thought Problems, Attention Problems, Rule-Breaking Behavior, and Aggressive Behavior). The CBCL T-score is a standardized score that compares a child's behavior to normative data from a reference population. A T-score of 50 represents

the average, while scores above 65 may indicate clinical concern for behavioral or emotional problems[21].

Assessment of comorbid conditions

The Kiddie Schedule for Affective Disorders and Schizophrenia—Present and Lifetime version (K-SADS-PL) is a widely used semi-structured psychiatric interview tool used to assess psychiatric disorders in children and adolescents. Two researchers conducted these interviews with all parents. The psychometric properties of the K-SADS-PL have shown high inter-rater reliability (κ=0.93) and test-retest reliability (intraclass correlation coefficients=0.74-0.90), with prior research demonstrating excellent reliability and validity[22]. Each item was rated as "present", "absent", or "uncertain", and the diagnostic algorithm followed international guidelines. This diagnostic interview has consistently demonstrated good inter-rater reliability and high concurrent validity across multiple studies[23].

Assessment of ASD traits

The Infant Behavior Checklist-Revised (IBC-R) is a 24-item parent-reported questionnaire used to assess autistic traits in early childhood and is widely used for children (2 years and older) and adolescents[24]. Each of the 24 items is rated on a binary scale, with higher scores indicating a greater number of problem behaviors. The IBC-R was developed by Kanai et al and administered to 97 children (68 with autism and 63 without; 97 males and 34 females; mean age, 4.1±2.2 years; range, 0.8-13.7 years) referred to psychiatric outpatient services. A cutoff score of 7 or higher indicated clinically significant autistic traits, with a false-negative rate of 16.9% and a false-positive rate of 15%. This analysis suggests that a total score of 7 or more is optimal for indicating clinically significant autistic traits. Psychometric analysis confirmed sufficient content and concurrent validity, with moderate internal consistency.

Assessment of attention deficit hyperactivity disorder (ADHD) traits

The Japanese version of the ADHD Rating Scale (ADHD-RS) was used to evaluate ADHD tendencies. This scale is based on the DSM-Ⅳ criteria for ADHD and comprises two subscales that measure inattention (nine items) and hyperactivity/impulsivity (nine items). Parents or guardians rated each item on a 4-point Likert scale ranging from 0 ("never or rarely") to 3 ("very often")[25]. Higher scores indicate stronger tendencies toward ADHD. The Japanese version of the ADHD-RS has demonstrated adequate reliability and validity[26].

Statistical analyses

Comparisons were made between the subthreshold hypomania group (n=32) and the clinical control group (n=249). Descriptive statistics (mean, standard deviation, median, range, and percentage) were calculated for demographic and clinical variables. The Mann-Whitney U test was used to compare continuous variables, and Fisher's exact test was used to compare categorical variables. To examine the correlation between subthreshold hypomanic symptoms and SPD, a forced-entry multiple regression analysis was conducted with the total SSP score as the dependent variable. The presence of subthreshold hypomanic symptoms was the primary independent variable. Additionally, the analysis was adjusted for covariates that were considered potential confounders based on their reported associations with SPD, including low income, sex, age at the time of assessment, and IBC-R, ADHD-RS, CBCL internalizing, and externalizing scores. Categorical variables (including subthreshold hypomanic symptoms, low income, and sex) were converted into dummy variables by assigning a value of 1 if the characteristic was present or the participant was male, and 0 otherwise, creating vectors of 1s and 0s. All data analyses were performed using the Statistical Package for Social Sciences version 26.0.0 (IBM Corp., Tokyo, Japan), and a two-sided

p-value <0.05 was considered statistically significant for all tests.

Results

After excluding children who met the criteria from the 334 children, the final number of children targeted was 281. They were included remained in the study and were categorized into those with subthreshold hypomanic symptoms (subthreshold hypomania group, n=32) and those children without such symptoms (clinical control group, n=249).

The subthreshold hypomania group comprised 32 children, accounting for 11.3% of the total sample. Of these, 6 children met the first criterion (hypomanic episodes lasting only 2-3 days) and 26 children met second criterion (hypomanic episodes with insufficient symptoms lasting at least 4 days).

The sociodemographic characteristics of the two groups are presented in Table 1. The proportion of low-income households was significantly higher in the subthreshold hypomania group than in the clinical control group (46.9% vs 18.1%).

The comorbidities of the two groups are presented in Table 2. The proportions of children with ASD (90.6% vs 63.9%), ADHD (40.6% vs 18.1%), oppositional defiant disorder (ODD; 31.3% vs 8.8%), and conduct disorder (CD; 34.3% vs 11.6%) were significantly higher in the subthreshold hypomania group.

Table 3 compares the IBC-R, ADHD-RS, and CBCL scores between the two groups. Both IBC-R (4.8 vs 2.2, $p<0.001$) and ADHD-RS scores (17.5 vs 10.4, $p=0.005$) were significantly higher in the subthreshold hypomania group than in the clinical control group. Furthermore, CBCL scores, including the total, externalizing, and internalizing scores, were all significantly higher in the subthreshold hypomania group.

A comparison of SPD prevalence and SSP scores is presented in Table 4. Fourteen children in the subthreshold hypomania group (43.8%) had SPD, which was significantly higher than the 30 children in the clinical control group (12.0%) ($p<0.0001$). Additionally, the total SSP score and scores on six of the seven sections (Tactile Sensitivity, Taste/Smell Sensitivity, Underresponsive/Seeks Sensation, Auditory Filtering, Low Energy/Weak, Visual/Auditory Sensitivity) were significantly higher in the subthreshold hypomania group than in the clinical control group (13.0 vs 10.1, $p=0.006$; 7.9 vs 5.9, $p=0.014$; 15.9 vs 9.0, $p<0.001$; 17.5 vs 10.6, $p<0.001$; 14.1 vs 10.1, $p=0.001$; 8.3 vs 6.6, $p=0.044$).

Table 5 presents the results of forced-entry multiple regression analysis. The total SSP score was

Table 1. Participant sociodemographic

	Total	Subthreshold hypomania group	Clinical control group	p
	n=281	n=32	n=249	
Sex, male	147 (52.1)	17 (53.1)	130 (52.2)	1.000[a]
Age (years)	12.2±2.7	11.9±2.9	12.3±2.6	0.288[b]
Years of parental education (years)	14.3±1.8	14.2±1.5	14.3±1.8	0.837[b]
Parental absence	68 (24.1)	11 (34.3)	57 (22.9)	0.187[a]
Low income	60 (21.3)	15 (46.9)	45 (18.1)	<0.001*[a]

Values are presented as n (%) or mean±standard deviation.

*Statistically significant differences ($p<0.05$).

[a]fisher's exact test.

[b]Mann-Whitney U test.

Table 2. Participant comorbidity

	Total	Subthreshold hypomania group	Clinical control group	p
	n=281	n=32	n=249	
ASD	188 (67.0)	29 (90.6)	159 (63.9)	0.002*
K-SADS-PL diagnoses				
Major depressive disorder	39 (13.9)	6 (18.8)	33 (13.3)	0.415
Dysthymia	6 (2.1)	1 (3.1)	5 (2.0)	0.519
Adjustment disorder	41 (14.5)	3 (9.4)	38 (15.3)	0.594
Anxiety disorders	101 (35.9)	16 (50.0)	85 (34.1)	0.116
Panic disorder	5 (2.0)	1 (3.1)	4 (1.6)	0.456
Separation anxiety disorder	6 (2.1)	3 (9.4)	3 (1.2)	0.021*
Social phobia	57 (20.2)	8 (25.0)	49 (19.7)	0.487
Generalized anxiety disorder	57 (20.2)	9 (28.1)	48 (19.3)	0.247
Obsessive-compulsive disorder	16 (5.7)	3 (9.4)	13 (5.2)	0.421
Post-traumatic stress disorder	1 (0.3)	1 (3.1)	0 (0.0)	0.114
Specific phobia	26 (11.0)	4 (12.5)	22 (8.8)	0.503
ADHD	58 (20.6)	13 (40.6)	45 (18.1)	0.005*
Oppositional defiant disorde	32 (11.4)	10 (31.3)	22 (8.8)	<0.001*
Conduct disorder	40 (14.2)	11 (34.3)	29 (11.6)	0.002*
Chronic motor or vocal tic disorder	15 (5.3)	1 (3.1)	14 (5.6)	1
Tourette's disorder	15 (5.3)	3 (9.4)	12 (4.8)	0.392
Eating disorders	12 (4.3)	0 (0.0)	12 (4.8)	0.372

Values are presented as n (%).

*Statistically significant differences ($p<0.05$).

K-SADS-PL; Kiddie Schedule for Affective Disorders and Schizophrenia - Present and Lifetime version; ASD, autism spectrum disorder; and ADHD, attention-deficit/hyperactivity disorder fisher's exact test.

Table 3. CBCL T scores, IBC-R score, ADHD-RS score for the subthreshold hypomania and clinical control groups.

	Total	Subthreshold hypomania group	Clinical control group	p
	n=281	n=32	n=249	
CBCL T scores				
Problems (total)	65.1±9.8	73.8±10.6	64±9.1	<0.001*
Internalizing	66.7±10.3	71.6±10.4	66±10.1	0.005*
Externalizing	59.8±10.6	69.2±13.6	58.6±9.6	<0.001*
IBC-R score	2.4±3.8	4.8±4.3	2.2±3.7	<0.001*
ADHD-RS score	11.2±11.3	17.5±14.1	10.4±10.6	0.005*

Values are presented as mean±standard deviation.

*Statistically significant differences ($p<0.05$).

IBC-R, Infant Behavior Checklist-Revised; ADHD-RS, Attention-Deficit/Hyperactivity Disorder-Rating Scale-Ⅳ; and CBCL, Child Behavior Checklist.

Mann-Whitney U test.

predicted by the presence of subthreshold hypomanic symptoms ($B=12.628$, $p<0.001$), age at the time of assessment ($B=-1.421$, $p<0.001$), total IBC-R score ($B=-1.277$, $p<0.001$), internalizing score ($B=0.605$, $p<0.001$), and externalizing score ($B=0.293$, $p=0.015$).

Table 4. Comparison of the prevalence of SPD and SSP scores between the subthreshold hypomania and clinical control groups.

	Total	Subthreshold hypomania group	Clinical control group	p
	n=281	n=32	n=249	
Sensory processing disorder , n(%)	44 (15.6)	14 (43.8)	30 (12.0)	<0.001*[a]
SSP scores, mean (SD)				
Total	59.1±22.0	81.1±34.4	56.3±18.0	<0.001*[b]
Tactile sensitivity	10.4±4.5	13.0±6.2	10.1±4.0	0.006*[b]
Taste/smell sensitivity	6.1±3.6	7.9±4.9	5.9±3.4	0.014*[b]
Movement sensitivity	3.9±1.9	4.4±2.9	3.9±1.8	0.469[b]
Underresponsive/seeks sensation	9.8±4.9	15.9±8.3	9.0±3.6	<0.001*[b]
Auditory filtering	11.4±5.7	17.5±7.6	10.6±4.9	<0.001*[b]
Low energy/weak	10.6±5.8	14.1±7.2	10.1±5.4	0.001*[b]
Visual/auditory sensitivity	6.8±3.3	8.3±5.4	6.6±2.9	0.044*[b]

Values are presented as n (%) or mean±standard deviation.

*Statistically significant differences ($p<0.05$).

SPD, sensory processing disorder; and SSP, Short Ssensrory Pprofile.

[a]fisher's exact test.

[b]Mann-Whitney U test.

Table 5. Results of multiple regression analysis showing predictors of SSP total scores

Variable	B	SE	β	p	95% CI (B)	VIF
Constant	16.794	9.637		0.083	−2.177 to 35.766	
Subthreshold hypomania	12.628	3.592	0.183	<0.001*	5.557 to 19.7	1.208
Age (year)	−1.421	0.405	−0.171	<0.001*	−2.219 to −0.623	1.053
Gender, male	−3.183	2.174	−0.073	0.144	−7.462 to 1.097	1.094
Low income	2.968	2.637	0.056	0.261	−2.223 to 8.158	1.083
IBC-R score	1.277	0.294	0.222	<0.001*	0.698 to 1.855	1.162
ADHD-RS score	0.122	0.097	0.063	0.213	−0.07 to 0.314	1.117
Internalizing T scores (CBCL)	0.605	0.117	0.284	<0.001*	0.375 to 0.835	1.339
Externalizing T scores (CBCL)	0.293	0.12	0.142	0.015*	0.058 to 0.529	1.492

Statistically signifificant differences ($p<0.05$). $R^2=0.371$.

ADHD-RS, Attention-Defificit/Hyperactivity Disorder-Rating Scale-Ⅳ; β, standardized partial regression coeffificient; B, unstandardized coeffificient. CBCL, Child Behavior Checklist; CI, confifidence interval; IBC-R, Infant Behavior Checklist-Revised; SE, standard error; SSP, Short Sensory Profifile; and VIF, variance inflation factor.

Discussion

To the best of our knowledge, this is the first study to demonstrate an association between subthreshold hypomanic symptoms and SPD in clinically referred children and adolescents. Our findings suggest that approximately 40% of children with subthreshold hypomanic symptoms also have SPD and that these symptoms are strongly associated with SPD severity.

Parker et al[13] suggested that adults with subthreshold hypomanic symptoms might display SPD, though their study was limited to those aware of these changes. In contrast, our study found that 40% of children with these symptoms had SPD, a higher prevalence than the control group. This may be due to the younger age of our participants, as SPD is known to diminish with age[27], and our study

relied on parent evaluations, which tend to be more reliable than self-reports[28]. Even after adjusting for confounding factors like socioeconomic status, age, and comorbidities, the association between subthreshold hypomanic symptoms and SPD remained significant, supporting its robustness.

The causal relationship between subthreshold hypomanic symptoms and SPD remains unclear; however, emotional dysregulation may be a contributing factor. Emotional dysregulation refers to the inability to regulate heightened emotions such as anxiety[29]. Fornaro et al[14] suggested that individuals with subthreshold hypomanic symptoms may exhibit state anxiety and impulsivity as well as SPD similar to those seen in individuals with manic symptoms. Children with SPD and those with subthreshold hypomanic symptoms tended to experience emotional dysregulation[30], suggesting that SPD may be involved in subthreshold hypomanic symptoms through emotional dysregulation. Another possible cause is biological factors. Previous research indicates shared risk factors, such as premature birth[31,32], and brain dysfunctions in regions like the cortex and amygdala[33,34].

In this study, the prevalence of subthreshold hypomanic symptoms in children was 11%, higher than the 5% typically reported in general population studies[35], but lower than the 10%-22% found in high-risk groups like children of parents with bipolar disorder[6,36]. Given the clinical population of our sample, these results align with expectations.

Additionally, children with subthreshold hypomanic symptoms had higher prevalence rates of ASD, ADHD, ODD, and CD and significantly higher levels of ASD and ADHD traits and externalizing problems. This is consistent with previous research, which showed that subthreshold hypomanic symptoms and these comorbidities share common genetic mutations related to impulse control and reward processing[37,38] and that they tend to follow similar clinical trajectories[39-41].

SPD assessments may help identify children with subthreshold hypomanic symptoms more effectively. Okada et al[42] noted that speech patterns in children with ASD resemble the pressured speech seen in mania, while their social behaviors also mirror hypomanic traits. Similarly, symptoms like hyperactivity and irritability, common in ADHD, ODD, and CD, overlap with manic symptoms, complicating diagnosis[40]. Since psychiatric evaluations rely on subjective interviews, children with subthreshold hypomanic symptoms, who often lack self-awareness, are hard to assess accurately. SPD assessments, based on objective sensory processing measures, could provide a more reliable method for identifying these symptoms, especially since SPD can be detected early in childhood, potentially resolving this diagnostic challenge.

Interventions for SPD in children with subthreshold hypomanic symptoms could help prevent future psychiatric disorders. Although these children face a poor prognosis, effective interventions remain scarce[1]. However, treatments like sensory integration therapy and cognitive-behavioral therapy (CBT) have shown promise for SPD[43-45]. Children with SPD often struggle with sensory processing, leading to anxiety and behavioral issues[46], which limit their social interactions and ability to learn emotional regulation[47,48]. Interventions for SPD in children with subthreshold hypomanic symptoms may reduce maladaptive behaviors and stress in daily life and decrease the number of maladaptive situations in social settings. McMahon et al[49] have suggested that treating SPD in early childhood could alleviate emotional dysregulation and potentially prevent anxiety disorder.

This study has several limitations. First, as it was conducted in a single university hospital with a clinically referred pediatric population, caution is needed when generalizing the results. Second, owing to its cross-sectional design, this study could not establish a causal relationship between subthreshold hypomanic symptoms and SPD; thus, further longitudinal studies are warranted.

Third, although this study suggests that evaluating SPD could help prevent future psychiatric issues in children with subthreshold hypomanic symptoms, it is important to consider the potential for reporting bias and limitations of the assessment methods. Nevertheless, this study was conducted in a clinical population that closely mirrored real-world clinical practice, suggesting that its findings are highly reproducible. Another strength of this study is the use of semi-structured interviews based on the DSM-5 diagnostic criteria, allowing for an accurate assessment of the characteristics of children with subthreshold hypomanic symptoms.

In conclusion, this study provides evidence supporting our initial hypothesis that subthreshold mania is associated with SPD in both children and adolescents. Since children with subthreshold hypomanic symptoms may often have SPD, it is necessary to assess SPD in order to administer appropriate interventions to children with subthreshold hypomanic symptoms. Future studies should investigate whether shared neurobiological mechanisms explain the association between subthreshold hypomanic symptoms and SPD. Additionally, longitudinal research is needed to determine how SPD evaluation and intervention may help prevent psychiatric disorders in children with these symptoms.

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References

1. Salazar de Pablo G, Cabras A, Pereira J, et al. Predicting bipolar disorder Ⅰ/Ⅱ in individuals at clinical high-risk: results from a systematic review. J Affect Disord 2023;325:778-786.
2. Beekman RAL, Ten Have M, de Graaf R, et al. Course of subthreshold manic symptoms and related risk factors in the general population: a three-year follow-up study. Bipolar Disord 2023;25:148-157.
3. Vaudreuil CAH, Faraone SV, Di Salvo M, et al. The morbidity of subthreshold pediatric bipolar disorder: a systematic literature review and meta-analysis. Bipolar Disord 2019;21:16-27.
4. Goldstein BI, Strober M, Axelson D, et al. Predictors of first-onset substance use disorders during the prospective course of bipolar spectrum disorders in adolescents. J Am Acad Child Adolesc Psychiatry 2013;52:1026-1037.
5. Serretti A, De Ronchi D, Olgiati P. Irritable mood and subthreshold hypomanic episodes correlate with more severe major depression. Neuropsychobiology 2021;80:425-436.
6. Papachristou E, Oldehinkel AJ, Ormel J, et al. The predictive value of childhood subthreshold manic symptoms for adolescent and adult psychiatric outcomes. J Affect Disord 2017;212:86-92.
7. Afzal T, Hipolito JL, Jin L. A systematic review of misdiagnosis of pediatric bipolar disorder: assessments and recommendations. Res Child Adolesc Psychopathol 2024;52:659-670.
8. Dunn W, Westman K. The sensory profile: the performance of a national sample of children without disabilities. Am J Occup Ther 1997;51:25-34.
9. Ben-Sasson A, Carter AS, Briggs-Gowan MJ. Sensory over-responsivity in elementary school: prevalence and social-emotional correlates. J Abnorm Child Psychol 2009;37:705-716.
10. Fryar-Williams S, Strobel JE. Biomarker case-detection and prediction with potential for functional psychosis screening: development and validation of a model related to biochemistry, sensory neural timing and end organ performance. Front Psychiatry 2016;7:48.
11. Houghton DC, Stein DJ, Cortese BM. Review: Exteroceptive sensory abnormalities in childhood and adolescent anxiety and obsessive-compulsive disorder: a critical review. J Am Acad Child Adolesc Psychiatry 2020;59:78-87.
12. DeSerisy M, Hirsch E, Roy AK. The contribution of sensory sensitivity to emotional lability in children with ADHD symptoms. Evid Based Pract Child Adolesc Ment Health 2019;4:319-327.
13. Parker G, Paterson A, Romano M, et al. Suprasensory phenomena in those with a bipolar disorder. Australas Psychiatry 2018;26:384-387.
14. Fornaro M, Ventriglio A, De Pasquale C, et al. Sensation seeking in major depressive patients: relationship to sub-threshold bipolarity and cyclothymic temperament. J Affect Disord 2013;148:375-383.

15. Engel-Yeger B, Gonda X, Canepa G, et al. Sensory profiles as potential mediators of the association between hypomania and hopelessness in 488 major affective outpatients. J Affect Disord 2018;225:466-473.
16. Hackman DA, Farah MJ. Socioeconomic status and the developing brain. Trends Cogn Sci 2009;13:65-73.
17. OECD FAMILY DATABASE, oe.cd/fdb | 2. doi:10.1787/c69de229-en.
18. Amemiya A, Fujiwara T. Association of low family income with lung function among children and adolescents: results of the J-SHINE study. J Epidemiol. 2019;29:50-56.
19. Ahn RR, Miller LJ, Milberger S, et al. Prevalence of parents' perceptions of sensory processing disorders among kindergarten children. Am J Occup Ther 2004;58:287-293.
20. Gourley L, Wind C, Henninger EM, et al. Sensory processing difficulties, behavioral problems, and parental stress in a clinical population of young children. J Child Fam Stud 2013;22:912-921.
21. Achenbach TM, Dumenci L. Advances in empirically based assessment: revised cross-informant syndromes and new DSM-oriented scales for the CBCL, YSR, and TRF: comment on Lengua, Sadowksi, Friedrich, and Fisher (2001). J Consult Clin Psychol 2001;69:699-702.
22. Kaufman J, Birmaher B, Brent D, et al. Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL): initial reliability and validity data. J Am Acad Child Adolesc Psychiatry 1997;36:980-988.
23. Tsuji H, Miyawaki D, Kawaguchi T, et al. Relationship of hypersensitivity to anxiety and depression in children with high-functioning pervasive developmental disorders. Psychiatry Clin Neurosci 2009;63:195-201.
24. Kanai C, Osada H, Koyama T, et al. A study of utility of Infant Behavior Checklist Revised (IBC-R) as a screening scale for pervasive developmental disorders. Rinsho Seishinigaku 2004;33:313-321. (In Japanese)
25. DuPaul G, Power T, Anastopoulos A, et al. ADHD Rating Scale-Ⅳ: checklists, norms, and clinical interpretation. In: Russell A. Barkley, editor. 1st ed. New York: Guilford Press, 1998.
26. Tani I, Okada R, Ohnishi M, et al. Japanese version of home form of the ADHD-RS: an evaluation of its reliability and validity. Res Dev Disabil 2010;31:1426-1433.
27. McCormick C, Hepburn S, Young GS, et al. Sensory symptoms in children with autism spectrum disorder, other developmental disorders and typical development: a longitudinal study. Autism 2016;20:572-579.
28. Gunderson J, Worthley E, Byiers B, et al. Self and caregiver report measurement of sensory features in autism spectrum disorder: a systematic review of psychometric properties. J Neurodev Disord 2023;15:5.
29. Gross JJ. Emotion regulation: affective, cognitive, and social consequences. Psychophysiology 2002;39:281-291.
30. Kelman J, Thacher A, Hossepian K, et al. Personality and pediatric bipolar disorder: toward personalizing psychosocial intervention. J Affect Disord 2020;275:311-318.
31. Niutanen U, Harra T, Lano A, et al. Systematic review of sensory processing in preterm children reveals abnormal sensory modulation, somatosensory processing and sensory-based motor processing. Acta Paediatr 2020;109:45-55.
32. Nosarti C, Reichenberg A, Murray RM, et al. Preterm birth and psychiatric disorders in young adult life. Arch Gen Psychiatry 2012;69:E1-E8.
33. Cha J, Speaker S, Hu B, et al. Neuroimaging correlates of emotional response-inhibition discriminate between young depressed adults with and without sub-threshold bipolar symptoms (Emotional Response-inhibition in Young Depressed Adults). J Affect Disord 2021;281:303-311.
34. Dutra SJ, Man V, Kober H, et al. Disrupted cortico-limbic connectivity during reward processing in remitted bipolar Ⅰ disorder. Bipolar Disord 2017;19:661-675.
35. Nielsen LG, Rimvall MK, Van Os J, et al. Precursors of self-reported subclinical hypomania in adolescence: a longitudinal general population study. PLoS One 2021;16:e0253507.
36. Duffy A, Goodday S, Keown-Stoneman C, et al. The emergent course of bipolar disorder: observations over two decades from the Canadian high-risk offspring cohort. Am J Psychiatry 2019;176:720-729.
37. Hosang GM, Lichtenstein P, Ronald A, et al. Association of genetic and environmental risks for attention-deficit/hyperactivity disorder with hypomanic symptoms in youths. JAMA Psychiatry 2019;76:1150-1158.
38. Taylor MJ, Ronald A, Martin J, et al. Examining the association between childhood autistic traits and adolescent hypomania: a longitudinal twin study. Psychol Med 2022;52:3606-3615.
39. Salazar de Pablo G, Guinart D, Cornblatt BA, et al. Demographic and clinical characteristics, including subsyndromal symptoms across bipolar-spectrum disorders in adolescents. J Child Adolesc Psychopharmacol 2020;30:222-234.
40. Fahrendorff AM, Pagsberg AK, Kessing LV, et al. Psychiatric comorbidity in patients with pediatric bipolar disorder—a systematic review. Acta Psychiatr Scand 2023;148:110-132.
41. Dell'Osso L, Carpita B, Bertelloni CA, et al. Subthreshold autism spectrum in bipolar disorder: prevalence and clinical correlates. Psychiatry Res 2019;281:112605.
42. Okada Y, Miyawaki D, Kusaka H et al. Subclinical manic symptoms in children with autism spectrum disorder.

Osaka City Med J 2016;62:103-110.
43. Pingale V, Fletcher TS, Candler C, et al. Effects of sensory diets: a single subject study. J Occup Ther Sch Early Interv 2022;15:165-180.
44. Schoen SA, Lane SJ, Mailloux Z, et al. A systematic review of ayres sensory integration intervention for children with autism. Autism Res 2019;12:6-19.
45. Weiss JA, Lunsky Y. Group cognitive behaviour therapy for adults with Asperger syndrome and anxiety or mood disorder: a case series. Clin Psychol Psychother 2010;17:438-446.
46. Chien CW, Rodger S, Copley J, et al. Sensory processing and its relationship with children's daily life participation. Phys Occup Ther Pediatr 2016;36:73-87.
47. Tomchek SD, Little LM, Dunn W. Sensory pattern contributions to developmental performance in children with autism spectrum disorder. Am J Occup Ther 2015;69:6905185040p1-6905185040p10.
48. Benarous X, Bury V, Lahaye H, et al. Sensory processing difficulties in youths with disruptive mood dysregulation disorder. Front Psychiatry 2020;11:164.
49. McMahon K, Anand D, Morris-Jones M, et al. A path from childhood sensory processing disorder to anxiety disorders: the mediating role of emotion dysregulation and adult sensory processing disorder symptoms. Front Integr Neurosci 2019;13:22.

Osaka City Med. J. Vol. 71, 73-82, 2025

The Association between Plasma Calprotectin and Infra-renal Aortic Calcification in Patients Undergoing Hemodialysis

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Abstract

Background

Vascular calcification is actively regulated by a balance between accelerators and inhibitors, and strongly associated with cardiovascular disease (CVD) events and mortality in patients with chronic kidney disease (CKD), as well as those undergoing hemodialysis. Recent report suggests that calprotectin, a proinflammatory factor also known as S100A8/A9 protein, may function to stimulate vascular calcification in CKD patients, though it remains unclear whether calprotectin is associated with vascular calcification in patients receiving hemodialysis treatments. The present study was conducted to examine the association of calprotectin with aortic calcification in that population.

Methods

Quantification of aortic calcification was performed using multi-slice computed tomography with the Agatston score. Plasma calprotectin levels were determined using a commercially available ELISA kit. The relationship between calprotectin and aortic calcification was analyzed using Spearman's rank correlation and multiple regression analysis.

Results

A total of 119 patients with a median age of 74 years (interquartile range: 66-80 years) were included. The median calprotectin level was 1089 ng/mL (interquartile range: 811-1639 ng/mL). Spearman's rank correlation revealed no significant correlation between calprotectin and aortic calcification ($\rho=0.029$, $p=0.753$). Furthermore, calprotectin was not shown to be an independent contributor to aortic calcification in multiple regression analysis ($\beta=0.086$, $p=0.320$).

Conclusions

In the present 119 patients undergoing hemodialysis, there was no significant association of

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plasma calprotectin level with aortic calcification found.

Key Words: Aortic calcification; Calprotectin; Cardiovascular disease (CVD); Hemodialysis

Introduction

Vascular calcification, commonly observed in patients with chronic kidney disease (CKD), has traditionally been recognized as a dystrophic process associated with atherosclerosis. However, emerging evidence suggests that it is actively regulated by various factors[1-3]. An imbalance between inhibitors, such as fetuin-A and matrix Gla protein, and promoters, such as bone morphogenic proteins, phosphate, matrix metalloproteases, and Runx2, likely accelerates vascular calcification[1,3,4]. As for the involved pathomechanism, decreased arterial elasticity due to calcification increases left ventricular hypertrophy, leading to heart failure, and also imparts excessive pulsatile energy to the microvasculature of target organs such as the brain and kidneys[5]. Clinically, vascular calcification is associated with poor cardiovascular disease (CVD) outcome[6]. Thus, prevention and/or reversal of vascular calcification is an urgent issue.

Calprotectin, often referred to as the hetero-complex of S100A8/A9, is primarily expressed in myeloid-origin cells, such as neutrophils and monocytes[7,8]. In response to inflammation and/or infection, calprotectin is released from neutrophils and monocytes, where it is abundant in cytoplasm. Since calprotectin is secreted in response to danger signals, it is classified as a damage-associated molecular pattern molecule, and also known as an alarmin. Furthermore, it interacts with pattern recognition receptors such as toll-like receptor 4 (TLR4) and receptor for advanced glycation end products (RAGE), with subsequent exertion of immunological effects. Consequently, calprotectin is considered to be associated with a wide range of inflammatory disorders, including CVD, inflammatory bowel disease, rheumatoid arthritis, and various types of cancer[7-10].

Recently, Amaya-Garrido et al presented findings demonstrating that calprotectin accelerates vascular calcification[11]. In that study, calprotectin was initially detected via proteome analysis in CKD patients with or without CVD events. To validate those findings, circulating calprotectin levels were measured, which revealed that higher calprotectin levels were associated with increased risk of mortality and CVD events in CKD patients, as well as greater vascular calcification in the epigastric artery of patients undergoing living-donor kidney transplantation. Furthermore, *in vitro* and animal experiments have clearly shown that calprotectin induces vascular calcification through TLR4 and RAGE. Nevertheless, it remains unclear whether calprotectin is associated with extent of vascular calcification.

The present study was conducted to investigate the association of plasma calprotectin level with infla-renal aortic calcification, quantified by multi-slice computed tomography (CT) findings, in patients undergoing hemodialysis.

Methods

Participants

This was a cross-sectional study of 119 patients undergoing hemodialysis at the Kidney Center of Shirasagi Hospital. Blood collection and abdominal CT scans were performed for all enrolled participants between December 2022 and December 2023. Clinical data were obtained from medical records and routine laboratory tests. Blood samples were drawn from an arteriovenous fistula just

prior to the first hemodialysis session of the week. Frozen plasma samples, including those used for calprotectin measurement, were stored at −80℃.

Hypertension was defined as blood pressure of 140/90 mm Hg or higher and/or use of any antihypertensive medication[12]. Dyslipidemia was defined as high-density lipoprotein cholesterol (HDL-C) ≦40 mg/dL, non-HDL-C ≧150 mg/dL, and/or use of statins[13]. Diabetes mellitus was defined as use of any antihyperglycemic medication and/or plasma glucose concentration ≧200 mg/dL at any time, or a previous diagnosis of diabetes. The exclusion criteria included a history of abdominal aortic aneurysm, aortic surgery, or aortic dissection as these conditions could cause hemodynamic and pressure changes affecting the aortic wall, potentially altering the levels of aortic calcification. History of CVD events was defined as past occurrence of ischemic heart disease, stroke, peripheral arterial disease, or intervention performed for arterial disease.

This study was conducted in accordance with the Declaration of Helsinki and Ethical Guidelines for Medical and Biological Research Involving Human Subjects presented by the Ministry of Health, Labor and Welfare of Japan (March 2021). The protocol was reviewed and approved by the Ethical Committee of Graduate School of Medicine, Osaka Metropolitan University (approval no. 2024-097). All participants provided written informed consent to participate in the study.

Quantification of aortic calcification

Infla-renal aortic calcification was determined as previously reported[14]. Briefly, images with a 0.8-mm slice thickness were obtained using an 80-slice CT scanner (Aquilion PRIME, Canon Medical Systems, Tochigi, Japan). Quantification of aortic calcification was performed using an image analysis workstation (Ziostation 2, Ziosoft Corporation, Tokyo, Japan) based on the Agatston score method[15]. The evaluation range extended from one slice above complete iliac artery bifurcation up to 100 mm. Calcification was defined as the volume of two adjacent pixels with a CT density exceeding 130 Hounsfield units within the aortic area as described above[14].

Measurement of plasma calprotectin

Plasma levels of human calprotectin were measured using an ELISA kit (Bio-Techne, DS8900) according to the manufacturer's protocol[11].

Statistical analysis

Data are expressed as median (interquartile range: IQR) or numbers (%). Correlations between various parameters and aortic calcification volume were examined using Spearman's rank correlation. The distributions of C-reactive protein (CRP) and aortic calcification volume were skewed, thus CRP was logarithmically transformed and aortic calcification volume was subjected to square root transformation. Multiple regression analysis was performed to assess whether calprotectin was an independent contributor to aortic calcification volume.

All statistical analyses were conducted using EZR[16] (version 1.55) (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria), a modified version of R Commander designed to add statistical functions frequently used in biostatistics. A p-value of <0.05 was considered to indicate statistical significance.

Results

The study flow diagram is shown in Figure 1. Of the 126 participants, 7 were excluded due to a history of abdominal aortic aneurysm (N=5), aortic surgery (N=1), or aortic dissection (N=1) as these

Table 1. Clinical characteristics

	All (n=119)
Age (years)	74 [66, 80]
Male / female (%)	72/47 (61/39)
Calprotectin (ng/mL)	1089 [811,1639]
Diabetes (%)	52 (44%)
Hypertension (%)	109 (92%)
Dyslipidemia (%)	61 (51%)
Current smoker (%)	9 (8%)
Cardiovascular disease events (%)	54 (45%)
Hemodialysis duration (years)	9.4 [8.2, 10.8]
Body mass index (kg/m^2)	22.2 [19.8, 25.2]
Serum albumin (g/dL)	3.5 [3.3, 3.6]
Serum creatinine (mg/dL)	9.4 [8.2, 10.8]
C-reactive protein (mg/dL)	0.22 [0.09, 0.65]
Calcium (mg/dL)	8.6 [8.3, 9.0]
Phosphate (mg/dL)	4.7 [4.0, 5.5]
Magnesium (mg/dL)	2.3 [2.2, 2.6]
Intact parathyroid hormone (pg/mL)	141 [104, 205]
Aortic calcification volume (mm^3)	6477 [3083, 9922]

Data are expressed as number, percentage, or median [interquartile range].

Table 2. Relationships of various factors with aortic calcification volume (Spearman's rank correlation)

Factor	ρ	p
Age (years)	0.281	0.002
Calprotectin (ng/mL)	0.029	0.753
Duration of hemodialysis (years)	0.054	0.562
Body mass index (kg/m^2)	0.002	0.983
Serum albumin (g/dL)	−0.047	0.612
Serum creatinine (mg/dL)	−0.054	0.558
C-reactive protein (mg/dL)	0.064	0.489
Serum calcium (mg/dL)	0.116	0.208
Serum phosphate (mg/dL)	−0.017	0.857
Serum magnesium (mg/dL)	−0.038	0.685
Intact parathyroid hormone (pg/mL)	0.070	0.449

ρ, Spearman's rank correlation coefficient.

conditions might affect the extent of aortic calcification. Clinical characteristics of the 119 participants are presented in Table 1. The median age was 74 years (IQR: 66-80)] and 72 (61%) were male. Among the present cohort, diabetes was present in 52 (44%), hypertension in 109 (92%), and dyslipidemia in 61 (57%), while 54 (45%) had a history of CVD events. The breakdown of CVD events included 9 cases of ischemic heart disease, 26 cases of stroke, and 2 cases of peripheral arterial disease. Seventeen cases had a combination of two or more of these conditions. Histograms indicating plasma calprotectin levels are shown in Figure 2. The median calprotectin level was 1089 ng/mL (IQR: 811-1639). Distributions of aortic calcification volumes and related square root values are shown in Figure 3A and 3B, respectively. Spearman's rank correlation revealed no significant

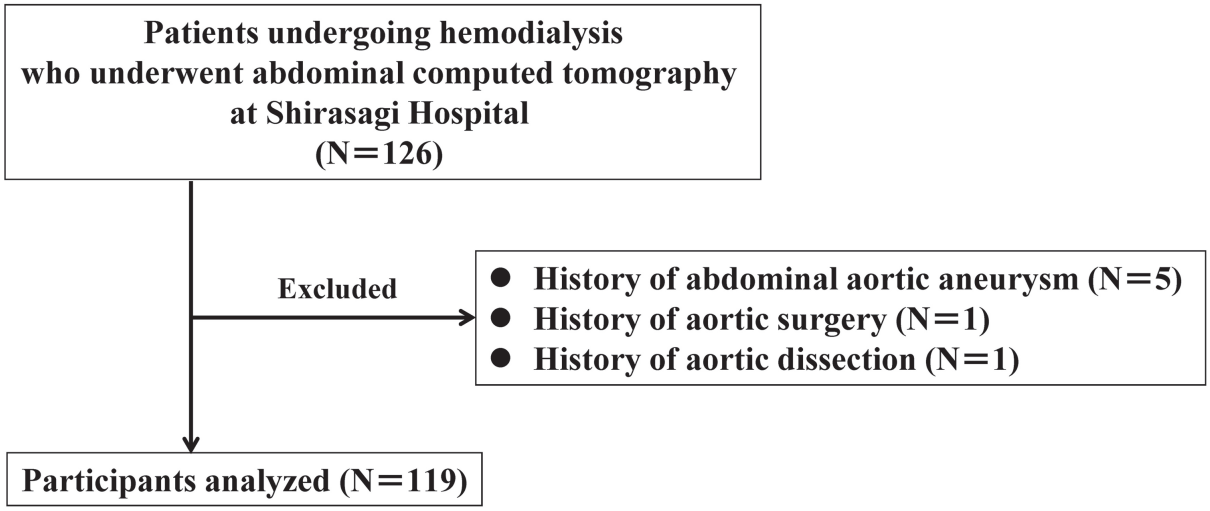

Figure 1. Selection of participants for the analysis.

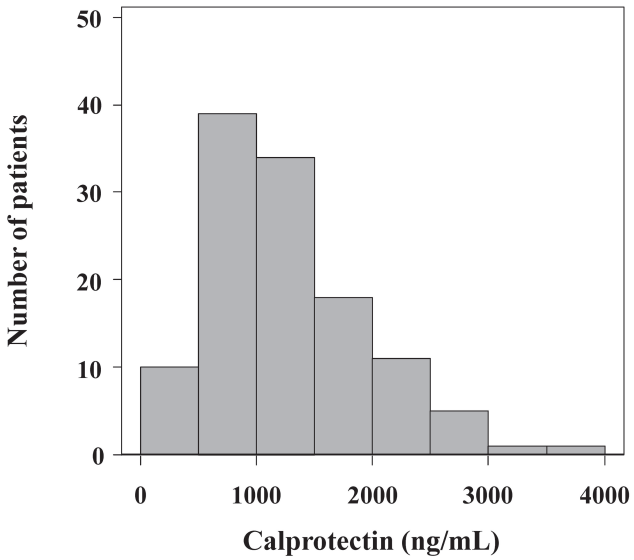

Figure 2. Histogram showing plasma calprotectin levels.

correlation between calprotectin level and aortic calcification volume (ρ=0.029, p=0.753) (Fig. 4), whereas age exhibited significant correlation (ρ=0.281, p=0.002) (Table 2).

Multiple regression analysis was used to examine the association of calprotectin level with aortic calcification volume, with adjustments for age, sex, duration of hemodialysis, history of CVD, diabetes, and traditional CVD risk factors (current smoking, hypertension, dyslipidemia) (Model 1), factors related to wasting and inflammation (serum albumin, body mass index, C-reactive protein) (Model 2), and factors related to CKD-mineral bone disorder (serum calcium, serum phosphate, serum magnesium) (Model 3). No significant association was found between calprotectin level and aortic calcification volume with any of the models (Table 3).

We also investigated whether CVD events influenced the association between calprotectin and aortic calcification. However, no significant association was found in either the presence or absence of

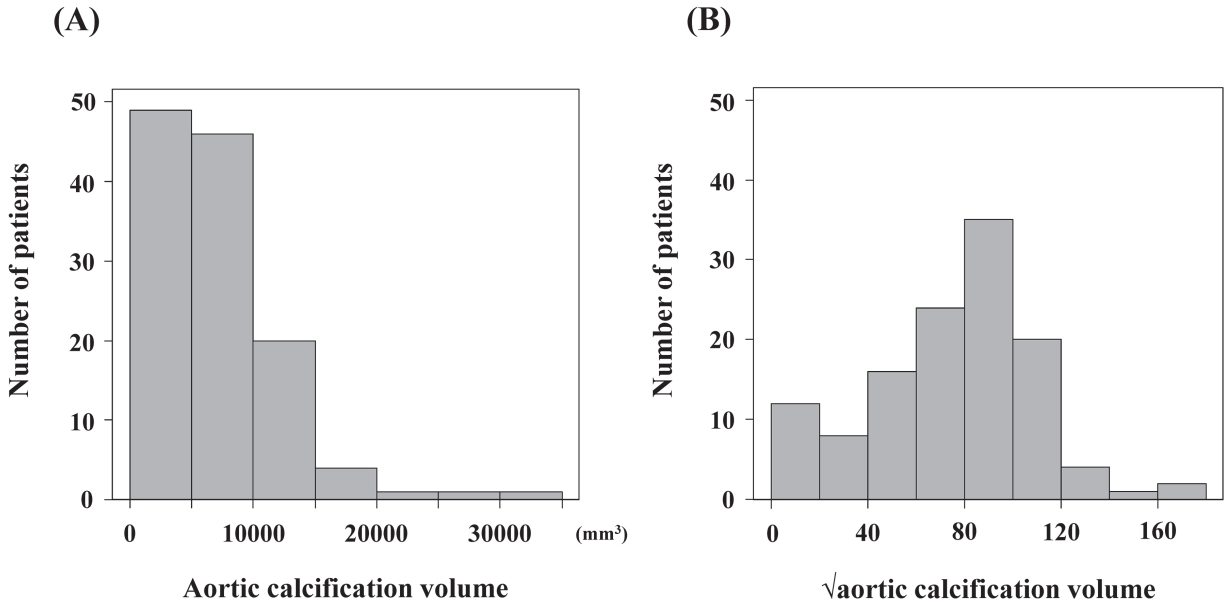

Figure 3. Distribution pattern of aortic calcification (A) and those square root values (B).

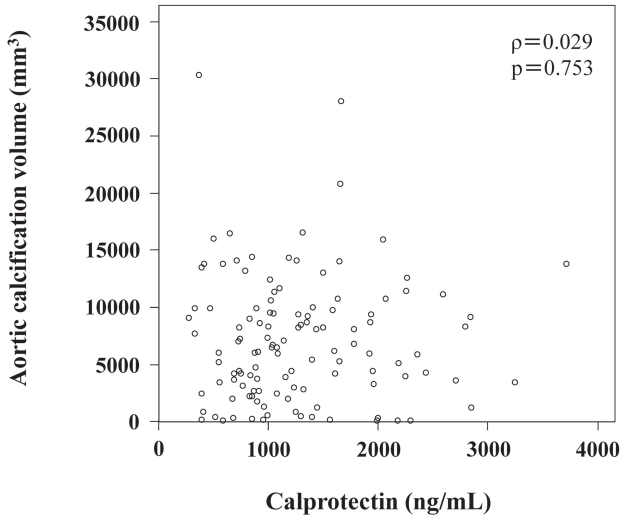

Figure 4. Scatter plots based on Spearman's rank correlation coefficient (ρ) showing relationship of calprotectin with aortic calcification volume.

CVD events (Fig. 5). Finally, we divided participants into three groups based on calcification volume: mild (<5000 mm^3), moderate (5000-10000 mm^3), and severe (10000-35000 mm^3). Again, no significant association between calprotectin and calcification was observed in any group (Fig. 6).

Discussion

The results of this cross-sectional study of 119 patients undergoing hemodialysis showed no significant association of plasma level of calprotectin, a factor related to exacerbation of vascular calcification, with aortic calcification, based on quantified evaluation using Agatston score.

Calprotectin (S100A8/A9) is secreted by neutrophils and macrophages, and known to be involved

Table 3. Multiple regression analysis of clinical factors including calprotectin possibly affecting aortic calcification volume

	Model 1		Model 2		Model 3	
Factor	β	p	β	p	β	p
Age (years)	0.388	<0.001	0.339	<0.001	0.397	<0.001
Sex (0=female, 1=male)	0.239	0.007	0.264	0.005	0.258	0.005
Duration of hemodialysis (years)	0.155	0.087	0.101	0.280	0.088	0.345
Cardiovascular disease events (yes=1)	0.202	0.021	0.177	0.049	0.160	0.078
Diabetes (yes=1)	0.062	0.512	0.095	0.328	0.124	0.192
Current smoker (yes=1)	0.234	0.006				
Hypertension (yes=1)	0.224	0.010				
Dyslipidemia (yes=1)	0.035	0.688				
Serum albumin (g/dL)			−0.053	0.586		
Body mass index (kg/m^2)			<0.001	0.999		
C-reactive protein (mg/dL)			0.076	0.445		
Serum calcium (mg/dL)					0.197	0.024
Serum phosphorus (mg/dL)					0.006	0.940
Serum magnesium (mg/dL)					−0.011	0.908
Calprotectin (ng/mL)	0.053	0.521	0.032	0.718	0.086	0.320
	R^2=0.269	p<0.001	R^2=0.163	p<0.001	R^2=0.191	p<0.001

β, standard regression coefficient; and R^2, multiple coefficients of determination.

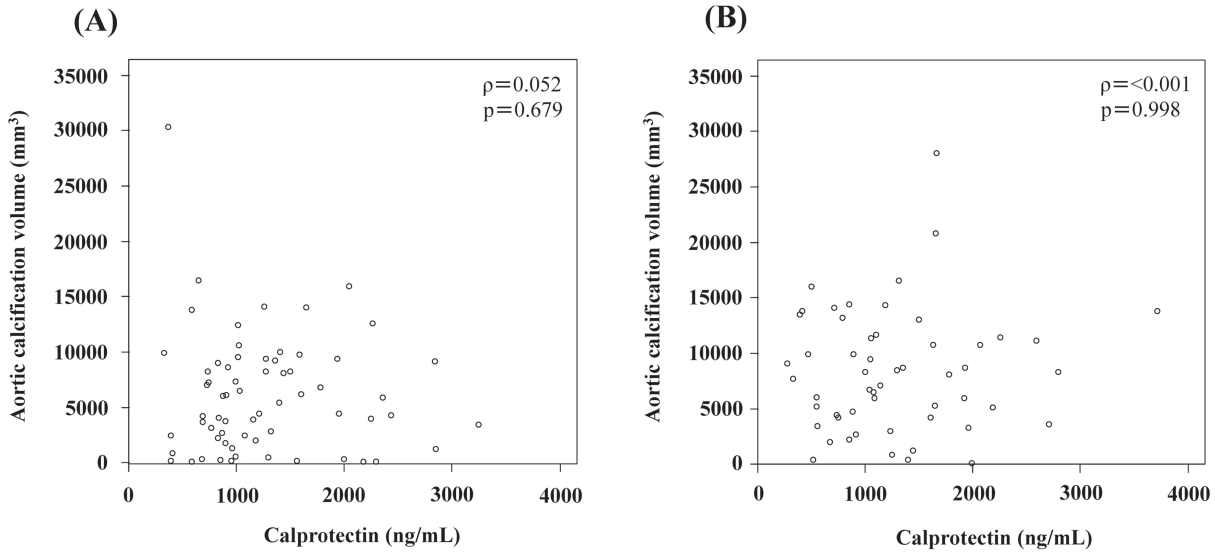

Figure 5. Scatter plots based on Spearman's rank correlation coefficient (ρ) showing relationship of calprotectin with aortic calcification volume in the absence (A) or the presence (B) of CVD events.

in various systemic inflammatory disorders, including CVD, inflammatory bowel disease, rheumatoid arthritis, and various types of cancer[7-10]. Recent study has also shown that calprotectin is associated with onset of CKD in the general population[17]. The study of Amaya-Garrido et al focused on patients with advanced CKD, and both *in vitro* and *in vivo* results demonstrated a direct effect of calprotectin on vascular calcification via TLR4 and RAGE[11]. Although their results showed that calprotectin findings could be used to predict CVD events and mortality in both patients with advanced CKD and

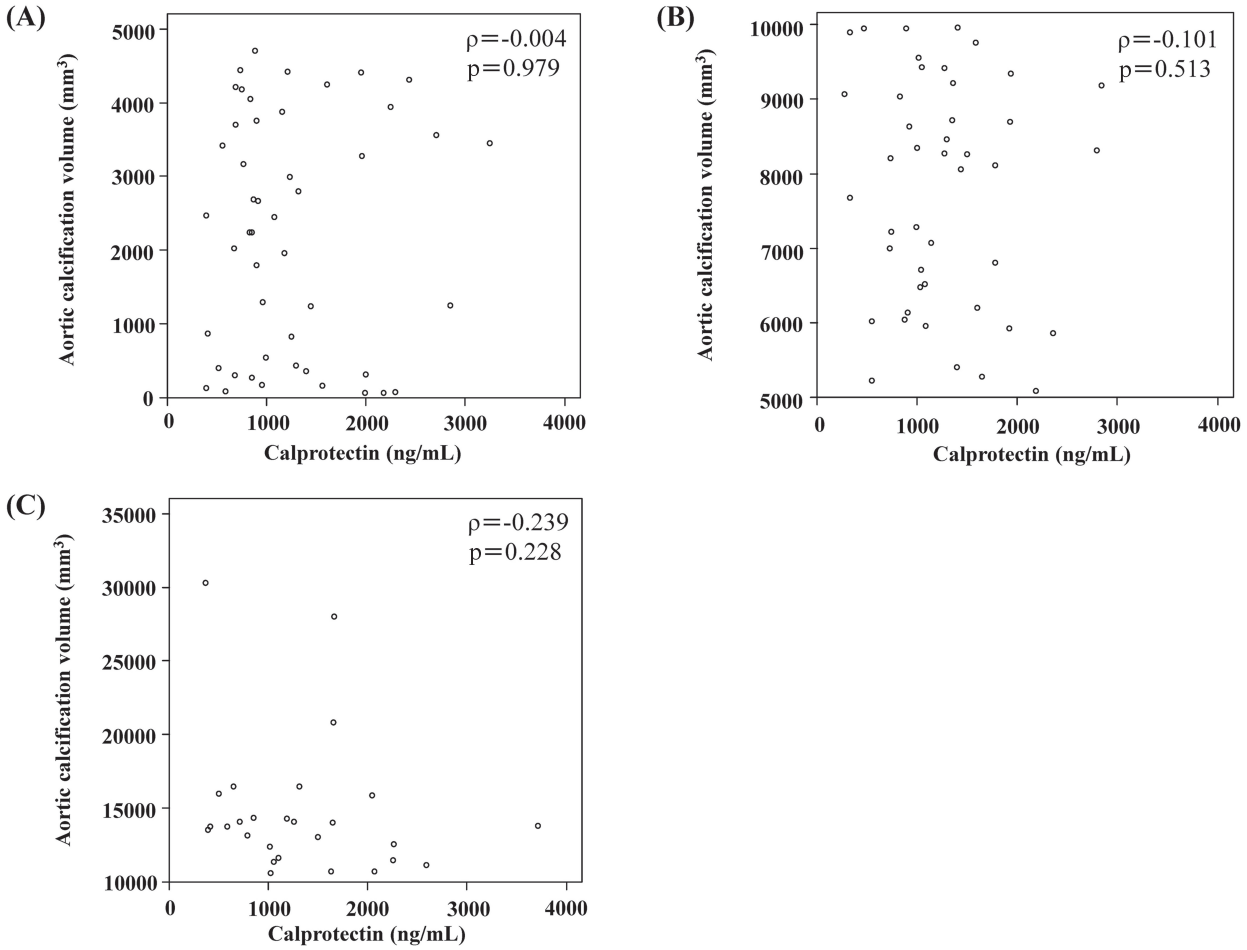

Figure 6. Scatter plots based on Spearman's rank correlation coefficient (ρ) showing relationship of calprotectin with aortic calcification volume according to the severity of calcification volume: (A) mild (<5000 mm^3), (B) moderate (5000-10000 mm^3), and (C) severe (10000-35000 mm^3).

those undergoing hemodialysis, vascular calcification was not quantified. The present study is the first to examine the association of calprotectin with aortic calcification in patients undergoing hemodialysis.

There are a few possible explanations for these results showing lack of a significant relationship between calprotectin and vascular calcification. Other critical calcification regulators, such as fetuin-A, matrix Gla protein (MGP), osteopontin, and osteoprotegerin[1], were not analyzed and it is possible that a more potent regulator may contribute to vascular calcification. Among these, MGP is sensitive to the effects of treatments for CVD and osteoporosis. MGP, which contains gamma-carboxylated residues, is activated through carboxylation by vitamin K[1]. Warfarin, a vitamin K antagonist, is widely used as an oral anticoagulant and is known to be associated with increased systemic calcification[18]. However, medication histories for these drugs were not available in this study. Additionally, the subjects in this study were limited to patients undergoing hemodialysis. Calprotectin was originally identified through proteomic analyses of non-dialyzed stage 3 to 4 CKD patients[11]. The authors of that study acknowledged that fetuin-A was not detected in the patients, despite its well-established role as a calcification inhibitor and also predictor of CVD and mortality in patients undergoing hemodialysis. Generally, patients receiving hemodialysis exhibit higher CRP levels as

compared to non-dialyzed CKD patients, as the procedure is known to recruit and activate neutrophils and monocytes on dialyzer membranes, leading to leukocytopenia[19,20]. Therefore, it is conceivable that calprotectin, produced as a result of membrane biocompatibility issues, may obscure the significant association of calprotectin with vascular calcification in patients undergoing hemodialysis.

The present study has a few limitations. First, the sample size was relatively small. Second, other calcification regulators including fetuin-A, MGP, osteopontin, and osteoprotegerin were not measured. Third, medication histories for warfarin, vitamin K, or other drugs that could regulate MGP activation were not available. Fourth, white blood cell count and differential data were not included. Fifth, we evaluated only infra-renal aortic calcification, and the association between calprotectin and calcification may differ in other regions of the aorta. Finally, due to the cross-sectional design, a causal relationship cannot be established from the results.

In conclusion, no significant association of plasma calprotectin level with aortic calcification, quantified using multi-slice CT findings, was found in examinations of 119 patients undergoing hemodialysis. Additional studies are warranted to determine whether calprotectin accelerates vascular calcification, with consideration of interactions with other calcification regulators in this patient population.

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References

1. Schlieper G, Schurgers L, Brandenburg V, et al. Vascular calcification in chronic kidney disease: an update. Nephrol Dial Transplant 2016;31:31-39.
2. Mori K, Emoto M, Inaba M. Fetuin-A: a multifunctional protein. Recent Pat Endocr Metab Immune Drug Discov 2011;5:124-146.
3. Mori K, Emoto M, Inaba M. Fetuin-A and the cardiovascular system. Adv Clin Chem 2012;56:175-195.
4. Basalyga DM, Simionescu DT, Xiong W, et al. Elastin degradation and calcification in an abdominal aorta injury model: role of matrix metalloproteinases. Circulation 2004;110:3480-3487.
5. Chirinos JA, Segers P, Hughes T, et al. Large-artery stiffness in health and disease: JACC state-of-the-art review. J Am Coll Cardiol 2019;74:1237-1263.
6. Goodman WG, London G, Amann K, et al. Vascular calcification in chronic kidney disease. Am J Kidney Dis 2004;43:572-579.
7. Pruenster M, Vogl T, Roth J, et al. S100A8/A9: from basic science to clinical application. Pharmacol Ther 2016; 167:120-131.
8. Montagnana M, Danese E, Lippi G. Calprotectin and cardiovascular events. A narrative review. Clin Biochem 2014;47:996-1001.
9. Sun Y, Xu H, Gao W, et al. S100a8/A9 proteins: critical regulators of inflammation in cardiovascular diseases. Front Cardiovasc Med 2024;11:1394137.
10. Ostrand-Rosenberg S, Huecksteadt T, Sanders K. The receptor for advanced glycation endproducts (RAGE) and its ligands S100A8/A9 and high mobility group box protein 1 (HMGB1) are key regulators of myeloid-derived suppressor cells. Cancers (Basel) 2023;15:1026.
11. Amaya-Garrido A, Brunet M, Buffin-Meyer B, et al. Calprotectin is a contributor to and potential therapeutic target for vascular calcification in chronic kidney disease. Sci Transl Med 2023;15:eabn5939.
12. Umemura S, Arima H, Arima S, et al. The Japanese society of hypertension guidelines for the management of hypertension (JSH 2019). Hypertens Res 2019;42:1235-1481.
13. Kinoshita M, Yokote K, Arai H, et al. Japan Atherosclerosis Society (JAS) guidelines for prevention of atherosclerotic cardiovascular diseases 2017. J Atheroscler Thromb 2018;25:846-984.
14. Ichii M, Ishimura E, Shima H, et al. Quantitative analysis of abdominal aortic calcification in CKD patients

without dialysis therapy by use of the Agatston score. Kidney Blood Press Res 2013;38:196-204.
15. Agatston AS, Janowitz WR, Hildner FJ, et al. Quantification of coronary artery calcium using ultrafast computed tomography. J Am Coll Cardiol 1990;15:827-832.
16. Kanda Y. Investigation of the freely available easy-to-use software 'EZR' for medical statistics. Bone Marrow Transplant 2013;48:452-458.
17. Bourgonje AR, Bourgonje MF, la Bastide-van Gemert S, et al. A prospective study of the association between plasma calprotectin levels and new-onset CKD in the general population. Kidney Int Rep 2024;9:1265-1275.
18. Poterucha TJ, Goldhaber SZ. Warfarin and vascular calcification. Am J Med 2016;129:635.
19. Losappio V, Franzin R, Infante B, et al. Molecular mechanisms of premature aging in hemodialysis: the complex interplay between innate and adaptive immune dysfunction. Int J Mol Sci 2020;21:3422.
20. Mori K, Kurajoh M, Inaba M, et al. Multifaceted nutritional disorders in elderly patients undergoing dialysis. Kidney and Dialysis 2023;3:1-23.

Osaka City Med. J. Vol. 71, 83-89, 2025

The Effectiveness and Potentials of 360-degree Virtual Reality for Learning Trauma Resuscitation and Resuscitative Procedures

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Abstract

Backgrounds

In recent years, the usefulness of virtual reality (VR) in simulation training and education has begun to be realized in the medical field. Since 2021, we conducted trauma education using VR for medical students and residents to learn trauma resuscitation and resuscitative procedures.

Methods

Since September 2023 to April 2024, we used VR for the lecture of trauma resuscitation and tube thoracostomy for tension pneumothorax as parts of the resuscitative procedure. A questionnaire on the lectures and pre- and post-lecture tests were given to evaluate the knowledge retention and procedural knowledges to evaluate the efficacy of VR materials. The survey with content formulated as Yes/No questions scored on a Likert scale of 1 to 5 was distributed to all students and physicians.

Results

During the study periods, the sequential 51 participants were included in this study. Scores for each question on how the sense of realism and immersion compared to a conventional lecture and how focused they were on the lecture were 5 (4-5). The questions on knowledge such as the participant's understanding of trauma resuscitation and of the indications and procedures for the skills and self-simulation for the skills also scored high points. However, the reason that they did not perform the actual procedures at this time, the questions about their self-confidence for the skills was indicated by the score of 3 (2-4).

Conclusions

VR lectures for medical students and residents are useful for retaining knowledge and learning procedures through immersion and concentration.

Key Words: Trauma resuscitation; VR; Virtual reality; Education; Simulation training

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Introduction

In the resuscitation of severe trauma patients, there is no time to waste. Past literature reported that for trauma patients with hypotension from hemorrhagic shock, every 3 minutes of additional time spent in the resuscitation room causes a 1% increase in mortality[1]. Other previous data also indicated that in patients who underwent laparotomy within 1 hour after admission, a 10-minute delay to the operation room was an independent factor of increased complications and poor prognosis[2].

In such tense situations, it is sometimes not easy for all staff to play their appropriate roles and establish communication as a unified trauma team. Thus, many trauma teams are making efforts to introduce simulations and individual off-the-job training. Unfortunately, however, the coronavirus disease 2019 (COVID-19) pandemic has caused cancellation or postponement of these training courses over the past few years. As well, during this period, medical students especially were forced to step aside from the red zone of clinical practice, and clinical studies for these students were obviously restricted at the global level[3-6].

Recently, virtual reality (VR) technology has advanced remarkably and is beginning to be used as an educational modality in the medical field. Several previous studies reported that lectures and simulations using VR are more efficient than conventional methods[6-8] and had the potential to lead to better memory retention and greater self-confidence in students[9,10]. However, most of this VR-based education consisted of, for example, complete simulations and surgical demonstrational training, and there have been almost no reports of VR-based education being used in the actual clinical setting.

From 2022, after installing a VR recording system in our resuscitation room as part of a multicenter study, we investigated the educational impacts of VR on the understanding of trauma care and resuscitation techniques of medical students and young physicians. In this study, we evaluated the effectiveness of this VR-based education with regards to trauma resuscitation and procedures for medical students and postgraduate year one and two medical doctors.

Methods

VR camera setting and recording

We installed a 360-degree VR camera produced by Jolly Good, Inc. (Tokyo, Japan) in the trauma resuscitation room in our hospital and recorded actual trauma resuscitation procedures (Fig. 1). Each patient's face was pixelated and their voice was altered to protect their privacy.

Viewing the recorded VR in lectures

Students and postgraduate year one and two physicians wore VR goggles so that multiple participants could view what the physicians saw at the same time. All participants participated in the same lecture about the principles of trauma resuscitation based on the Japan Advanced Trauma Evaluation and Care guidelines and learned the indications, material preparation, and performance of the decompression procedure and its complications for tension pneumothorax through VR. An internet system was set up within the hospital so that all participants could watch the VR recorded in the resuscitation room at the same time in the conference room (Fig. 2).

The lecture was provided by the same lecturer to avoid the human bias due to lecturers and technical advises.

As the content of the lecture, we adopted the obstructive shock due to tension pneumothorax, which was one of the most important aspects of trauma resuscitation.

Figure 1. The figures of the virtual reality set installed in our resuscitation room.
VR, virtual reality.

Figure 2. The snapshots during the lecture.

The main reason for adopting tension pneumothorax was that the pathology of tension pneumothorax was easy for students to understand, and tube thoracostomy was an important basic procedure in trauma that did not involve too many procedural steps and equipments.

Evaluation

A survey with content formulated as Yes/No questions scored on a Likert scale of 1 to 5 was distributed to all students and physicians. The questions in the survey included whether the participants enjoyed the VR lectures, how was the sense of realism and immersion compared to a conventional lecture, what was their understanding of the trauma resuscitation, how was the self-confidence or self-simulation for performing tube thoracostomy, and what were their expectations for such use of VR lectures in the future.

To evaluate their understanding of trauma resuscitation, indications, and procedures for tube thoracostomy to treat tension pneumothorax, the participants were assessed on their knowledge retention through 10-question pre- and post-course tests.

Ethics approval and consent for publication

This study had been authorized by the institutional review board of Osaka Metropolitan University. Authorization number is 2021-162. Written informed consent for publication was obtained from all of the participants. All methods were carried out in accordance with relevant institutional guidelines and regulations.

Statistical methods

As this was a pilot study, we did not perform statistical comparisons between the VR learning group and conventional learning group. To assess the effectiveness of the lecture, the differences between the pre- and post-test results were statistically evaluated using the Mann-Whitney U test. Continuous variables are described as the median (25%-75% interquartile range) due to non-normal distribution.

Results

From January 2024 to April 2024, subsequent 51 participants participated in the VR lecture. As the background data of the participants, twenty participants were 5th grade medical students, four participants were 6th grade medical students. Furthermore, twenty-two were postgraduate year one and five were postgraduate year two physicians. Thirty participants were male and the other twenty-one participants were female (Male: 58.8%).

Table 1 lists the survey responses. All of the participants answered that they had enjoyed the VR lectures. Scores for each question on how the sense of realism and immersion compared to conventional lecture, how the concentration for the lecture were all 5 (4-5) among the students and young physicians.

The questions about the knowledge such as understanding of the trauma resuscitation and understanding of the indications and procedures for the skills and self-simulation for the skills were also scored high points especially in young physicians.

As they had not performed actual procedures at this time, the question about the self-confidence for the skills was 2 (2-4) among the students and 3 (3-4) among the young physicians.

Table 2 shows the results of the 10-question pre- and post-training tests. They showed that the retention of knowledge after the lectures was effectively improved for all groups of participants. Regarding the preparation and equipment, although young physicians tended to have higher score

Table 1. Surveyed contents

Students	N=24
Enjoyed the VR lecture Yes / No	Yes: 24 (100%)
Focused on the lecture	5 (4-5)
Sense of realism and immersion	5 (4-5)
Understanding of the trauma resuscitation	4 (4-5)
Understanding of the indications and procedures for the skills	4 (3-5)
Self-simulation for the skills	4 (4-5)
Self-confidence for the skills	2 (2-4)
Young physicians (PGY 1-2)	N=27
Enjoyed the VR lecture Yes / No	Yes: 27 (100%)
Focused on the lecture	5 (4-5)
Sense of realism and immersion	5 (4-5)
Understanding of the trauma resuscitation	5 (4-5)
Understanding of the indications and procedures for the skills	4 (4-5)
Self-simulation for the skills	4 (4-5)
Self-confidence for the skills	3 (3-4)

PGY, post graduate year; and VR, virtual reality.

Table 2. The 10 question pre- and post- test results

	Pre score	Post	p-value
Total score	5 (4-7)	8 (7-9)	0.035
Students			N=24
About trauma resuscitation (3 questions)	1 (0-2)	2 (2-3)	
About preparation (2 questions)	1 (0-1)	1 (1-2)	
About equipment (2 questions)	0 (0-1)	2 (1-2)	
About procedure (2 questions)	1 (0-1)	2 (1-2)	
About complications (1 question)	1 (0-1)	1 (1-1)	
Young physicians (PGY 1-2).			N=27
About trauma resuscitation (3 questions)	1 (1-2)	3 (2-3)	
About preparation (2 questions)	1 (0-2)	2 (2-2)	
About equipment (2 questions)	1 (1-2)	2 (1-2)	
About procedure (2 questions)	1 (1-2)	2 (2-2)	
About complications (1 question)	1 (0-1)	1 (1-1)	

than medical students in the pre-test, after being taken the lecture, the medical students were able to achieve almost the same scores compared to the young physicians.

Their expectations for using such VR lectures in the future were high with the participants noting that it was easy to imagine actual procedures and interesting to observe the tension in the real clinical environment. The VR lectures improved their self-simulation for the skills, and they hoped such training would become standardized.

Discussion

With the advancement of medicine, the knowledge required of medical students is increasing year by year, and learning the content for national examination preparation is taking much more time. As well, it is also important for the students to experience and get a feeling for the clinical field earlier and to prepare for being exposed to clinical decision making or communicating with the patients and their family in the clinical setting. Through the use of a VR lecture, medical students were able to experience a very immersive feeling during the training, and they evaluated the VR lecture as making it easy to understand practical experiences and the procedures.

Clinical learning in medical education has changed over time[11]. Several decades ago, medical students directly learned about disease from patients invited to the lecture room[12]. But recently, VR has shown the potential to provide medical students with early clinical experiences and many kinds of simulations in the future and to become an effective new method of practical training[6-10].

Furthermore, in recent years, constraints are being placed on the time required to improve clinical abilities and acquire skills due to work style reforms. Young doctors must now train for their procedures and acquire clinical experience in much more efficient way. Under these circumstances, the usefulness of simulation education and surgical training using VR has begun to be reported worldwide[13-16]. Clarke described in a systematic review of 16 studies from 140 titles that VR training for orthopedic surgery trainees can develop their skills and give them confidence[17].

With regard to the education needed to treat severe trauma, although reliable and rapid clinical decision making and procedure execution are required, the number of encounters with such trauma is not so frequent. By using VR based on actual clinical recorded simulations, we believe it may be useful for multi-professional simulations, case debriefings, and learning team management and non-technical skills. Furthermore, we also think that VR-based simulation has the potential to simulate medical care and treatment required in rare situations such during disasters or conflicts.

Limitations

There are future challenges to overcome in verifying the effects of VR. One limitation of this preliminary study is that it did not have a comparison target, so it will be important to verify the results of VR training in comparison with those of traditional lectures and simulations. Based on this research, it will be necessary to continue using VR in lectures and simulations and evaluate the usefulness of VR in education and simulation training.

We conclude that VR lectures for medical students and residents are useful for retaining knowledge and learning procedures through immersion and concentration. They might be helpful to increase interest and understanding of diseases in the field of medical practice.

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References

1. Clarke JR, Trooskin SZ, Doshi PJ, et al. Time to laparotomy for intra-abdominal bleeding from trauma does affect survival for delays up to 90 minutes. J Trauma 2002;52:420-425.
2. Meizoso JP, Ray JJ, Karcutskie CA 4th, et al. Effect of time to operation on mortality for hypotensive patients with gunshot wounds to the torso: the golden 10 minutes. J Trauma Acute Care Surg 2016;81:685-691.
3. Jhajj S, Kaur P, Jhajj P, et al. Impact of Covid-19 on medical students around the globe. J Community Hosp

Intern Med Perspect 2022;12:1-6.
4. Wang W, Li G, Lei J. The impact of COVID-19 on medical students. GMS J Med Educ 2024;41:Doc10.
5. Ferrel MN, Ryan JJ. The impact of COVID-19 on medical education. Cureus 2020;12:e7492.
6. Dedeilia A, Sotiropoulos MG, Hanrahan JG, et al. Medical and surgical education challenges and innovations in the COVID-19 era: a systematic review. In Vivo 2020;34:1603-1611.
7. Reznick RK, MacRae H. Teaching surgical skills--changes in the wind. N Engl J Med 2006;355:2664-2669.
8. Beqari J, Seymour NE. Application of technology to educational needs in surgery. J Surg Oncol 2021;124:181-192.
9. Vávra P, Roman J, Zonča P, et al. Recent development of augmented reality in surgery: a review. J Healthc Eng 2017;2017:4574172.
10. Nomura T, Mamada Y, Nakamura Y, et al. Laparoscopic skill improvement after virtual reality simulator training in medical students as assessed by augmented reality simulator. Asian J Endosc Surg 2015;8:408-412.
11. Drees BM, Omurtag K. Accelerated medical education: past, present and future. Mo Med 2012;109:352-356.
12. Howe A, Anderson J. Involving patients in medical education. BMJ 2003;327:326-328.
13. Elzie CA, Shaia J. A pilot study of the impact of virtually embodying a patient with a terminal illness. Med Sci Educ 2021;31:665-675.
14. Izard SG, Juanes JA, García Peñalvo FJ, et al. Virtual reality as an educational and training tool for medicine. J Med Syst 2018;42:50.
15. Barteit S, Lanfermann L, Bärnighausen T, et al. Augmented, mixed, and virtual reality-based head-mounted devices for medical education: systematic review. JMIR Serious Games 2021;9:e29080.
16. Holla M, Berg MVD. Virtual reality techniques for trauma education. Injury 2022;53:S64-S68.
17. Clarke E. Virtual reality simulation-the future of orthopaedic training? A systematic review and narrative analysis. Adv Simul (Lond) 2021;6:2.

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Cortical Superficial Siderosis in Patients with Dementia is Associated with Poor Activities of Daily Living

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Abstract

Background

Cortical superficial siderosis (cSS) is characterized by hemosiderin deposition along the leptomeninges that cover the cerebral cortex. The clinical significance of cSS, occasionally associated with Alzheimer's disease, remains unclear. This study investigated the impact of cSS on activities of daily living along with clinical and imaging findings in patients with dementia.

Methods

From April 2018 to March 2023, we retrospectively enrolled patients with dementia attending a memory clinic whose magnetic resonance imaging (MRI)-confirmed cSS and age- and sex-matched patients without cSS. The instrumental activities of daily living (IADL) scores, cognitive test results, neurological findings, and MRI findings were assessed.

Results

A total of 26 patients with cSS (mean age 79±6 years, 13 men and 13 women) and 26 control patients were analyzed. The IADL scores were significantly lower in the cSS group than those in the control group ($p<0.01$). Delusion was more frequently observed in the cSS group, although overall cognitive function did not differ significantly between the groups. MRI revealed that cerebral microbleeds occurred more frequently in the cSS group (23%) than in the control group (4%).

Conclusions

Although cSS does not significantly impair general cognitive function, it can negatively affect activities of daily living and social cognition. Targeted management of daily functional impairments is essential for patients with cSS.

Key Words: Cerebral amyloid angiopathy; Cerebral microbleed; Head trauma; Delusion; Memory disturbance

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Introduction

Cortical superficial siderosis (cSS) is defined as hemosiderin deposition over the cortical layer, which typically results from chronic bleeding into the subarachnoid space[1-3]. Due to the expanded use of iron-sensitive magnetic resonance imaging (MRI), cSS is being identified with increasing frequency[4]. Unlike infratentorial superficial siderosis, in which gait ataxia and hearing loss are common clinical manifestations, the clinical implications of cSS have not been comprehensively assessed[5]. In older populations, the most commonly reported cause of cSS is cerebral amyloid angiopathy (CAA), followed by aneurysms, arteriovenous malformations, and head trauma, whereas infratentorial superficial siderosis is primarily attributed to cervical spine duropathy[5].

To clarify the clinical significance of cSS, we evaluated its impact on activities of daily living along with associated clinical and imaging findings.

Methods

Study design

From April 2018 and March 2023, we retrospectively enrolled patients with dementia who attended the Memory Clinic of Kosaiin Hospital, Osaka, and whose MRI findings revealed cSS. Age- and sex-matched patients without cSS on MRI who attended the clinic during the same period served as controls. For age match, dementia patients with closest birthday were chosen.

Ethical consideration

The study protocol was approved by the Institutional Review Board of Kosaiin Hospital (approval #2020-7). An opt-out consent process for retrospective epidemiological study participation was completed by all patients or their family members at the initial outpatient visit.

Risk analysis and cause of dementia

The potential risk factors for superficial siderosis and cerebrovascular disease, including hypertension, diabetes mellitus, dyslipidemia, medication use, and trauma history, were assessed. Dementia etiology was determined based on the International Working Group 2 criteria for Alzheimer's disease[6], American Heart Association/American Stroke Association criteria for vascular cognitive impairment[7], and the 2017 revised consensus criteria for dementia with Lewy bodies[8].

Neurological Examination

Cognitive functions, including orientation, memory, calculation, visuospatial skills, executive function, and speech, were evaluated, along with the Mini-Mental State Examination (MMSE) and Revised Hasegawa Dementia Scale (HDS-R), by experienced neurologists (T.Y., M.T., or M.K.).

Instrumental activities of daily living (IADL) were scored to assess complex daily tasks including financial management, meal preparation, housekeeping, transportation, telephone use, medication management, and shopping[9]. IADL, rather than basic activities of daily living (BADL) which represents simple daily tasks, such as bathing and toileting, is recognized as a sensitive measure of complex functional abilities for individuals with mild cognitive impairment, Alzheimer's disease[10] and other types of dementia.

Neuroimaging

The T2*-weighted image sequence of MRI was used to assess cSS, cerebral microbleeds, and other intracerebral hemorrhages. Cerebral atrophy in the hippocampus and across cortical regions was evaluated using the voxel-based specific regional analysis system for Alzheimer's disease, an online software tool[11]. White matter lesions were evaluated using fluid attenuated inversion recovery

(FLAIR) images.

Statistical analysis

Statistical analyses were performed using the chi-square test to compare the frequencies of abnormalities between the two groups. A p-value of less than 0.05 was considered statistically significant.

Results

Demographic data

Twenty-six patients with cSS (mean age 79±6 years, 13 men and 13 women) and 26 age- and sex-matched controls were enrolled (Table 1). Among the risk factors for dementia and stroke, diabetes mellitus was more prevalent in the non-cSS group ($p<0.05$), whereas dyslipidemia was more common in the cSS group ($p<0.05$).

Although traumatic subarachnoid hemorrhage is a recognized cause of cSS, history of a major head injury was present in only 8% of the patients with cSS and 4% of patients without cSS. Neck trauma, which has been linked to cervical dural damage causing classical superficial siderosis, was not reported in either group. Similarly, clinical history of subarachnoid hemorrhage, potentially

Table 1. Characteristics of the study population

	cSS group	non-cSS group	p value
N	26	26	
Age	79±6	79±6	
Men: Women	13:13	13:13	
Hypertension	58% (15)	46% (12)	n.s.
Marital Status			
Married	69% (18)	77% (20)	n.s.
Divorced	12% (3)	8% (2)	n.s.
Widowed	19% (5)	16% (4)	n.s.
Drinking Status			
Daily	35% (9)	27% (7)	n.s.
Social	23% (6)	31% (8)	n.s.
None	42% (11)	42% (11)	n.s.
Diabetes Mellitus	3.8% (1)	23% (6)	$p<0.05$
Dyslipidemia	38% (10)	12% (3)	$p<0.05$
Antithrombotic Drugs	12% (3)	19% (5)	n.s.
Use of Lecanemab	0% (0)	0% (0)	n.s.
History of Head Trauma	8% (2)	4% (1)	n.s.
Neck Trauma	0% (0)	0% (0)	n.s.
Subarachnoid Hemorrhage	8% (2)	8% (2)	n.s.
Cerebral Infarction	0% (0)	0% (0)	n.s.
Intracerebral Hemorrhage	24% (6)	8% (2)	n.s.
Causes of Dementia			
Alzheimer's Disease	38% (10)	54% (14)	n.s.
Vascular Cognitive Impairment	38% (10)	38% (10)	n.s.
Chronic Subdural Hematoma	16% (4)	0% (0)	$p<0.05$
Head Trauma	8% (2)	4% (1)	n.s.
Dementia with Lewy Bodies	0% (0)	4% (1)	n.s.

n.s., not significant; and cSS, cortical superficial siderosis.

Table 2. Cognitive and neurological findings

	cSS group	non-cSS group	p value
Subjective Symptoms			
Headache	0% (0)	0% (0)	n.s.
Transient Focal Neurologic Episodes	8% (2)	0% (0)	n.s.
Cognitive Findings			
Disorientation	69% (18)	77% (20)	n.s.
Memory Disturbance	81% (21)	100% (26)	$p<0.05$
Acalculia	8% (2)	8% (2)	n.s.
Aphasia	0% (0)	0% (0)	n.s.
Visuospatial Agnosia	31% (8)	23% (6)	n.s.
Construction Apraxia	15% (4)	15% (4)	n.s.
Executive Dysfunction	23% (6)	27% (7)	n.s.
Delusion	15% (4)	0% (0)	$p<0.05$
Hallucination	15% (4)	4% (1)	n.s.
Neurological Findings			
Hearing Disturbance	38% (10)	35% (9)	n.s.
Dysarthria	4% (1)	0% (0)	n.s.
Dysphagia	0% (0)	0% (0)	n.s.
Muscle Weakness	0% (0)	0% (0)	n.s.
Sensory Disturbance	0% (0)	0% (0)	n.s.
Gait Disturbance	8% (2)	8% (2)	n.s.

n.s., not significant; and cSS, cortical superficial siderosis.

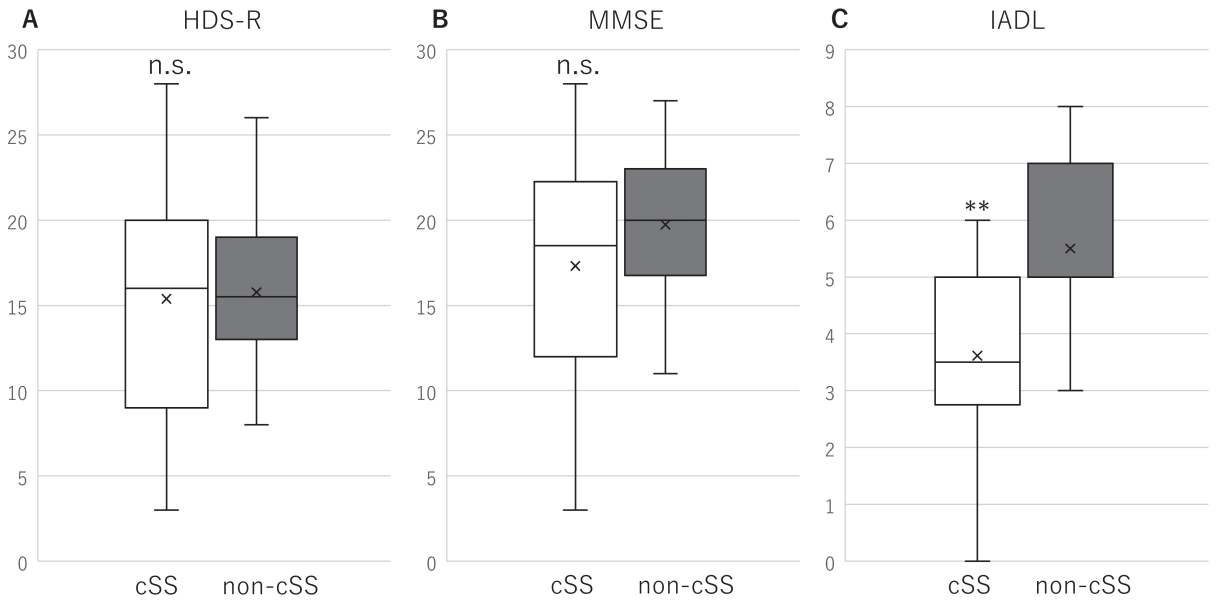

Figure 1. Assessment of cognitive function and activities of daily living. The HDS-R (A) and MMSE (B) show no significant differences between groups. However, the IADL scores (C) are significantly lower for the cSS group compared to the non-cSS group. ** $p<0.01$. n.s., not significant; MMSE, Mini-Mental State Examination; HDS-R, Revised Hasegawa Dementia Scale; IADL, instrumental activities of daily living; and cSS, cortical superficial siderosis.

associated with cSS, was present in 8% of the patients in both groups.

Intracerebral hemorrhage, frequently occurring in patients with CAA, was observed in 24% of cSS cases compared to 8% of non-cSS cases; however, this difference was not statistically significant.

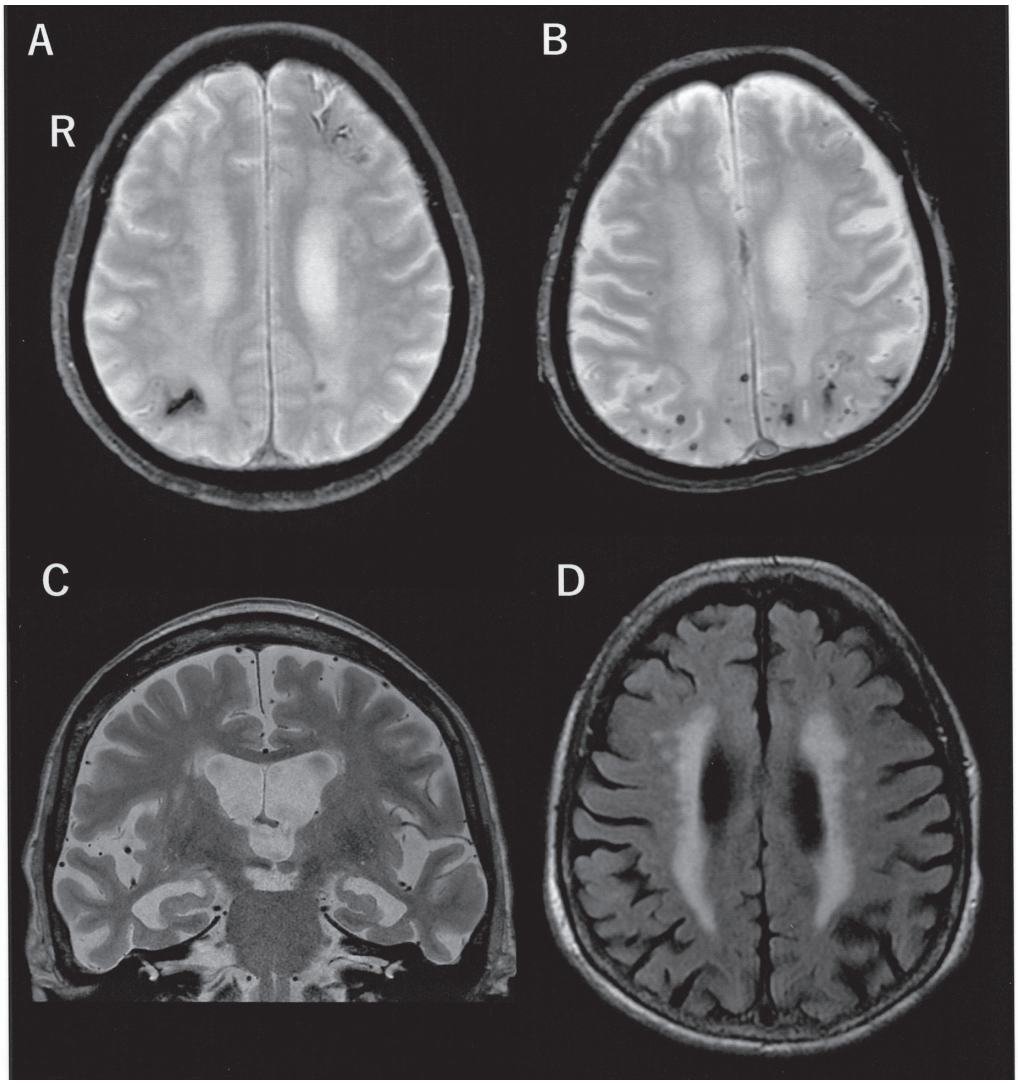

Figure 2. Representative magnetic resonance imaging (MRI) findings of patients with cortical superficial siderosis (cSS). A T2*-weighted image reveals cSS in the left frontal and right parietal lobes (A). Multiple cerebral microbleeds are evident in the bilateral parietal lobes on T2*-weighted images (B). Marked hippocampal atrophy is observed in a coronal section of a T2-weighted image (C). White matter lesions are observed on a fluid-attenuated inversion recovery (FLAIR) image (D). R, right. MRI, magnetic resonance imaging; and cSS, cortical superficial siderosis.

Background disease

The causes of dementia in the two groups are summarized in Table 1. Alzheimer's disease was the most prevalent cause in both the cSS (38%) and non-cSS (42%) groups, followed by vascular cognitive impairment, which accounted for 38% of the patients in each group. Notably, chronic subdural hematoma was the third most common cause of dementia in the cSS group (16%), whereas no such cases were observed in the non-cSS group ($p<0.05$). Although a definitive diagnosis of head trauma-related dementia was present in only 8% of the cSS group, undetected episodes of head trauma may have been the primary underlying cause of cSS in this study.

Subjective symptoms

No significant headaches were reported in either group (Table 2). Transient focal neurological episodes, commonly associated with CAA and named amyloid spells[12], were observed in 8% of those in the cSS group, and 0% of those in the non-cSS group.

Table 3. Summary of magnetic resonance imaging findings

	cSS group	non-cSS group	p value
Location of Siderosis			
Frontal	50% (13)	None	
Temporal	42% (11)	None	
Parietal	35% (9)	None	
Occipital	38% (10)	None	
Cerebral Microbleeds	23% (6)	4% (1)	$p<0.01$
Hippocampal Atrophy †	2.10±1.19	1.74±0.96	n.s.
Global Atrophy †	8.09±3.37	7.50±3.57	n.s.
White-matter Lesions	38% (10)	54% (14)	n.s.

† Calculated with voxel-based specific regional analysis system for Alzheimer's disease. cSS, cortical superficial siderosis

Cognitive findings

Most cognitive functions were comparably impaired among the two groups; however, memory disturbances were slightly more frequent in the non-cSS group (Table 2). In contrast, delusion was significantly more common in the cSS group ($p<0.05$).

Neurological findings

Hearing impairment, which is often linked to classical superficial siderosis involving the auditory nerve, was present in both groups at similar rates (38% cSS group; 35% non-cSS group). No other specific focal neurological deficits were observed in either group.

Cognitive tests and activities of daily living tests

Figure 1 presents the HDS-R, MMSE, and IADL assessment results. Although the HDS-R and MMSE scores were similarly affected in both groups, the IADL scores were significantly lower in the cSS group than in the non-cSS group ($p<0.01$).

Neuroimaging

Figure 2 presents the representative MRI findings for the patients with cSS, including cSS and cerebral microbleeds on T2*-weighted images, hippocampal atrophy on a T2-weighted image, and white matter lesions on a FLAIR image.

A summary of the MRI findings is displayed in Table 3. Cortical siderosis was frequently observed in the frontal (50%), temporal (42%), parietal (35%), and occipital (38%) cortices. MRI detected cerebral microbleeds more frequently in the cSS group (23%) than in the non-cSS group (4%). Hippocampal atrophy was mild in both groups, and white matter lesions were found at similar rates.

Discussion

This study demonstrated that cSS in patients with dementia was associated with head injury, as a probable underlying cause, along with clinical manifestations of delusion, characteristic neuroimaging findings of cerebral microbleeds, and most notably, impaired IADL.

In this study, global cognitive function, as measured using the HDS-R and MMSE, did not differ significantly between the cSS and non-cSS groups, although the IADL scores were lower in the cSS group. The IADL assesses complex daily functions such as meal preparation, housekeeping, telephone use, transportation, shopping, and financial management[9]. These activities rely not only on advanced cognitive abilities but also on psychiatric health. Given the higher incidence of delusion in the cSS

group, these psychiatric symptoms may have contributed to reduced IADL performance.

The mechanisms of cSS that affect cognitive and psychiatric functions vary according to the underlying cSS causes. Hemosiderin accumulation on the cerebral cortex, frequently observed in cSS, directly induces neuronal degeneration[1]. In classical superficial siderosis, hemosiderin accumulation in the posterior fossa results in deafness and cerebellar ataxia, affecting the auditory nerve and cerebellum[1]. Oral iron-chelating agents can help mitigate symptom progression by reducing hemosiderin deposition[1]. Unlike classical superficial siderosis, cSS is considered secondary siderosis[1]. The conditions associated with cSS that may impair cognitive function include CAA, head trauma, aneurysms, other vascular diseases, and anticoagulant therapy.

CAA is the primary cause of cSS, particularly in older individuals with Alzheimer's disease[13]. Clinically, CAA can lead to stroke, particularly lobar intracerebral hemorrhage, headache with meningeal signs, and transient focal neurological episodes (known as amyloid spells). CAA is strongly associated with dementia, mainly due to Alzheimer's disease pathology and, to a lesser extent, vascular events. On MRI, CAA presents with cerebral lobar hemorrhages, cerebral microbleeds, cortical microinfarcts, and cSS. Intracerebral hemorrhages, cerebral microbleeds[14], and transient focal neurological episodes were more frequent in the cSS group, implicating CAA as a primary driver of cSS and a potential contributor to cognitive and psychiatric impairments. On the contrary, Alzheimer's disease was diagnosed equally in the cSS and non-cSS groups.

Chronic subdural hematoma and head trauma were also more frequently observed in the cSS group than in the non-cSS group, suggesting that head trauma may be a secondary leading cause of cSS, with traumatic pathology potentially contributing to neurological dysfunction.

In the present study, the cortical siderosis distributed widely, not associated with the cortical cognitive dysfunction beneath the siderosis (Table 3). Similarly, cSS was not associated with hippocampal atrophy nor with global atrophy (Table 3). Although cSS is a powerful biomarker for poor IADL, the direct damaging effects of cSS may be limited.

Other vascular pathologies, apart from CAA, were not more prevalent in the cSS group than in the non-cSS group. No cases of reversible cerebral vasoconstriction syndrome were identified. Although antithrombotic medications can induce cSS, their usage did not differ significantly between the groups. Additionally, lecanemab, an anti-amyloid β antibody recently introduced for early Alzheimer's disease and mild cognitive impairment, can induce localized subarachnoid hemorrhage[15]; however, none of the patients in this study had been treated with this medication.

The limitations of this study include the (1) small sample size, (2) retrospective design, (3) high proportion of patients with vascular cognitive impairment, and (4) heterogeneity in the cSS pathophysiology. The direct effects of cSS on cognitive function and IADL may be evaluated more accurately in larger and more homogeneous sample populations, allowing for subgroup analyses. Further studies are warranted to address these limitations.

In summary, this study demonstrated that cSS was an independent risk factor for impaired IADL in patients with dementia. Targeted management of psychiatric symptoms may be essential for optimizing the care of patients with cSS.

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References

1. Kumar N. Superficial siderosis: a clinical review. Ann Neurol 2021;89:1068-1079.
2. Charidimou A, Boulouis G, Greenberg SM, et al. Cortical superficial siderosis and bleeding risk in cerebral amyloid angiopathy: a meta-analysis. Neurology 2019;93:e2192-e2202.
3. Charidimou A, Boulouis G, Roongpiboonsopit D, et al. Cortical superficial siderosis and recurrent intracerebral hemorrhage risk in cerebral amyloid angiopathy: large prospective cohort and preliminary meta-analysis. Int J Stroke 2019;14:723-733.
4. Pongpitakmetha T, Fotiadis P, Pasi M, et al. Cortical superficial siderosis progression in cerebral amyloid angiopathy: prospective MRI study. Neurology 2020;94:e1853-e1865.
5. Kumar N. Beyond superficial siderosis: introducing "duropathies". Neurology 2012;78:1992-1999.
6. Dubois B, Feldman HH, Jacova C, et al. Advancing research diagnostic criteria for Alzheimer's disease: the IWG-2 criteria. Lancet Neurol 2014;13:614-629.
7. Gorelick PB, Scuteri A, Black SE, et al. Vascular contributions to cognitive impairment and dementia: a statement for healthcare professionals from the american heart association/american stroke association. Stroke 2011;42:2672-2713.
8. McKeith IG, Boeve BF, Dickson DW, et al. Diagnosis and management of dementia with Lewy bodies: fourth consensus report of the DLB Consortium. Neurology 2017;89:88-100.
9. Lawton MP, Brody EM. Assessment of older people: self-maintaining and instrumental activities of daily living. Gerontologist 1969;9:179-186.
10. Tekin S, Fairbanks LA, O'Connor S, et al. Activities of daily living in Alzheimer's disease: neuropsychiatric, cognitive, and medical illness influences. Am J Geriatr Psychiatry 2001;9:81-86.
11. Matsuda H, Mizumura S, Nemoto K, et al. Automatic voxel-based morphometry of structural MRI by SPM8 plus diffeomorphic anatomic registration through exponentiated lie algebra improves the diagnosis of probable Alzheimer disease. AJNR Am J Neuroradiol 2012;33:1109-1114.
12. Yamada M. Cerebral amyloid angiopathy: emerging concepts. J Stroke 2015;17:17-30.
13. Charidimou A, Peeters AP, Jäger R, et al. Cortical superficial siderosis and intracerebral hemorrhage risk in cerebral amyloid angiopathy. Neurology 2013;81:1666-1673.
14. Charidimou A, Boulouis G, Frosch MP, et al. The Boston criteria version 2.0 for cerebral amyloid angiopathy: a multicentre, retrospective, MRI-neuropathology diagnostic accuracy study. Lancet Neurol 2022;21:714-725.
15. van Dyck CH, Swanson CJ, Aisen P, et al. Lecanemab in early Alzheimer's disease. N Engl J Med 2023;388:9-21.

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