＊＊＊学術コーナー＊＊＊

荒尾市医師会学術講演会記録

1．集会　消化管画像診断研究会

日時　平成27年５月11日(月)午後７時～午後８時30分

会場　荒尾市医師会館

講演　○薬剤紹介　エフェイント（抗血小板剤）

冠動脈疾患のみアスピリンと併用

持続高血圧体重50kg以下注意

副作用　大出血1.9％、小出血38％

プラビックスは30％無効

○症例

1.70才♂OM.B10↓γ-GTP↑↑US肝牛様

2.72才♂高血圧＋C型胆道系↑USIHBD拡張 CT.左葉肝内胆管がん→肝切除へ

3.94才♀貧血GS.潰瘍近傍出血

4.60才♀貧血.下血出血性潰瘍＋MK→熊大ope

5.67才♂上･下咽頭・食道胃重複癌

1.2.牛島　3.4.福島　5.田宮

出席　３名

共催　荒尾市医師会、第一三共㈱

2．集会　「荒尾市医師会内科医会」特別講演会

日時　平成27年５月14日(木)午後７時

会場　ホテルヴェルデ

講演　《特別講演》

座長　鴻江病院　院長　鴻江和洋先生

『脳梗塞治療の最前線』

荒尾市民病院 神経内科部長 渡邉聖樹先生

出席　83名

共催　荒尾市医師会、荒尾市医師会内科医会

エーザイ株式会社

第２回荒尾市玉名郡市医師会合同学術講演会

レビー小体型認知症のケアと地域連携

平成27年３月６日　荒尾市医師会館

熊本大学大学院生命科学研究部　神経精神医学分野

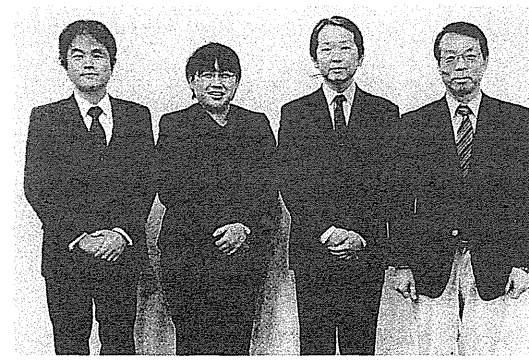
石川智久

□はじめに

レビー小体型認知症（Dementia with Lewy Bodies; DLB）は、疾患についての啓発がすすみ、臨床診断基準の策定、画像診断技術の向上、治療法の進歩などとも相まって、その頻度は神経変性性認知症疾患の上位を占めるまでになった。しかし、実際の臨床現場では、診断し治療を開始したその後の生活支援・暮らしのサポートについて、まだまだ試行錯誤がつづいている。本稿では、DLBの概念について簡潔にまとめた後、ケアをどう考えるかについて、また、地域連携の必要性について、考察したい。

□レビー小体型認知症の概念

レビ小体型認知症（Dementia with Lewy Bodies; DLB）の名称は、レビー小体（Lewy body）に由来する。レビー小体とは、1912年に神経学者のフレデリック・レビー（Frederic H. Lewy）によって発見された神経細胞内封入体である。レビーは、パーキンソン病（Parkinson's disease:PD）患者の、主に脳幹部にレ



レビー小体型認知症のケアと地域連携

ビー小体を発見したが、その後長年にわたり欧米では、「レビー小体はPD患者の中脳にみられ、大脳皮質には出現しないか出現しても少数である」とされた。したがって、PD患者には基本的には認知症は生じないとされ、仮に認知症がみられたとするならば、それはPDにアルツハイマー病（Alzheimer's disease:AD）が併発したものと解釈されていた。

1984年、小阪憲司は、パーキンソン症候と認知症を主症状とする症例の神経病理学的所見をまとめ、大脳皮質や扁桃体にもレビー小体が存在することを報告し、びまん性レビー小体型認知症（diffuse Lewy body disease:DLBD）の概念を提唱した。これにより、従来欧米で考えられていたPDと認知症との関連は大きく覆された。その後、レビー小体は、中脳、大脳皮質、大脳辺縁系、交感神経節など、随所で確認されるに至り、パーキンソン症状発症から1年以上経過して認知症をともなう「パーキンソン病に伴う認知症（Parkinson's disease with dementia:PDD)」といわれる症例も報告されるようになった。1995年、第1回国際ワークショップにおいて、それまで混乱していた疾患名称をDLBにすることがまとめられたが、現在では、PD、DLB、PDDを包括する概念として、「レビー小体病（Lewy Body Disease)」の名称が提唱されている。

□レビー小体型認知症のケア

DLBは、PDの一面として神経症候（振戦・寡動・歩行障害など）および自律神経症状（起立性低血圧や便秘など）と、認知症の一面として認知機能低下（注意障害、記憶障害、判断力低下、失見当識）や精神症候（幻覚・妄想、抑うつ、不安など）とを併せ持つ特徴がある。それらに加えて、種々の一般身体合併症（肺炎、脱水、転倒骨折、発汗、栄養不良、食欲低下、睡眠障害など）をともなうため、ケアにおいては、現在の症状がどの領域の症候なのかを整理しながら評価し、対処すべき症候の優先順位はどのようになるのかを見極めることがポイントである。

＜認知機能変動＞

認知機能が大きく変動するケースでは、状態に合わせてケア・リハビリを導入する。状態の悪い時には無理に介入せず、危険な行動がないかを観察する。状態が良い時には積極的なリハビリテーションを行う。変動であるので、時間がたてば自然とよくなることを家族にも伝える。特に注意障害の強い場合は、転倒に留意する。環境設定は、もっとも状態が悪い時を基準に環境整備するのがよい。

＜パーキンソニズム＞

転倒に注意するとともに、抗精神病薬をふくむ薬剤過敏性があるため、投薬内容に留意する。また、抗パーキンソン薬投薬開始時にも幻覚・妄想などの副作用に留意する。嚥下機能低下をきたしている場合には誤嚥に留意する。

＜幻視・錯視＞

壁や天井のしみ、無造作に積み重ねた座布団、脱いだままにした服などは、幻視、錯視をおこしやすい。部屋はできるだけ整理整頓して不要な物を撤去するなどして、刺激を少なくする工夫を行う。幻視を訴える際には、否定するのではなく、さりげなく安心する声掛けを心がける。

＜夜間の行動障害＞

DLBでは、その前駆症状または示唆的特徴として、レム睡眠行動障害（REM sleep behavior disorder:RBD）や、夜間の大声の寝言などがみられる。日中の活動性を高め、自然な睡眠をうながす工夫を行う。デイサービスの活用は効果的である。本人・家族が怪我をしないよう、家具の角を保護する、寝床の周囲に物を置かない、などといった工夫をおこなう。

＜身体症状への対応＞

誤嚥、不顕性の誤嚥性肺炎、極度の脱水や栄養不良など、身体状態が容易に悪化し、しばしば緊急を要する事態になりうるため、ケアだけでなく、医療・看護の介入を常に念頭に置く。自律神経症状が目立つケー

スでは、強度の便秘や起立性低血圧による失神・意識消失に注意し、必要に応じて医療の介入をおこなう。

□レビー小体型認知症と地域連携

前述のとおり、DLBの病態は、神経症候、精神症候と、種々の身体疾患合併の３領域にまたがる。そのため、各領域の医療連携が不可欠である（図１）。神経内科領域では、パーキンソン症状、自律神経症状の管理、精神科領域では、幻覚、妄想、認知機能への対応、本人や家族への心理面のケア、各身体科では、各々の身体科治療が必要となるが、とくにパーキンソン関連薬と精神科関連薬とは、薬効と副作用とが互いに影響しあうため、その調整には医師間での情報提供を密に行うことが重要である。

さらには、医療と看護、介護との情報共有も重要であり、急な脱水や食欲低下、肺炎、発熱、転倒骨折など緊急を要する事態の対応をふくめて、常日頃から家族本人、ケアマネージャーなどと連携することが必要である（図２）。

図１

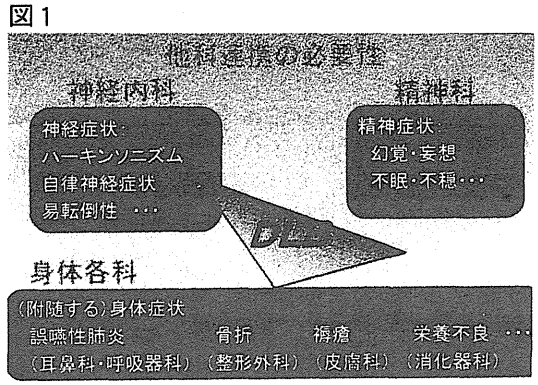
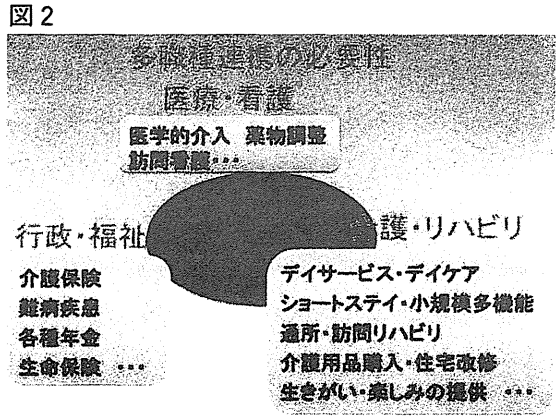


図２



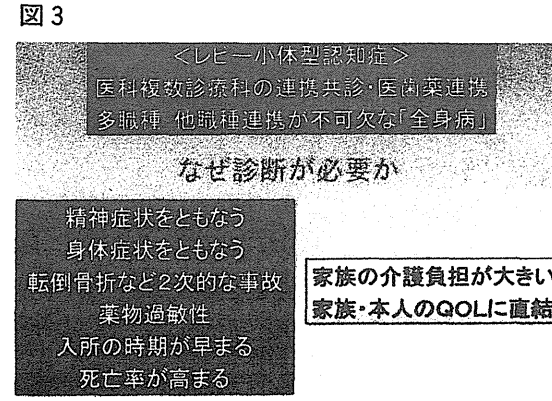
□おわりに

DLBの臨床診断基準は2005年第３回国際ワークショップにより最新版が策定され、我々は臨床症候からDLBを診断することができるようになった。診断ができるということは、治療という意味でも、連携を図る意味でも、患者家族の生活の質（QOL）を高める意味でも、非常に大きな意義がある。DLBはその状態像が、神経症状、精神症状、各種の身体疾患を附随するため、単一の診療科だけで対応できる疾患ではなく、心身を含めたいわば「全身病」としてとらえるべき疾患である。また、日常生活支援やケアの場面においては、医療・看護・介護福祉の連携も必要であり、医科・歯科・薬科も含めた包括的在宅生活支援が実践できる疾患ともいえる（図３）。さらに、治療薬として、2014年に本邦において、塩酸ドネペジル（アリセプト®）の適応が承認された。神経変性疾患であるので、病状は緩徐に進行するが、一時的であれ、塩酸ドネペジルの効果は早くて１週間で実感できる。そういった観点では、臨床医にとって「よくなった」という実感の持てる数少ない認知症のひとつである。

《参考となる資料》

「トーク　認知症　－臨床と病理－」
小阪憲司・田邉敬貴：著、医学書院、2007.
「レビー小体型認知症の臨床」
小阪憲司・池田　学：著、医学書院、2010.

図３



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「内科医のための　認知症治療　はじめの一歩」浦上克哉：編、羊土社、2014.

荒尾市医師会内科医会特別講演会
2015年5月14日

脳梗塞治療の最前線

荒尾市民病院神経内科　渡邉聖樹

脳梗塞超急性期治療の目的は、病的血栓を溶解し、機能障害をきたしているが不可逆的損傷に至っていない虚血性ペナンブラを救済すること。血流改善は経静脈的血栓溶解と血管内治療があり、それぞれ発症から4.5時間以内、8時間以内が適応となるが、残存するペナンブラが少なければ、発症からの時間が短くても適応外となってしまう。再開通治療が実施される多くの症例が発症から120分以内である。経静脈血栓溶解療法は、大きな血栓、すなわち近位部閉塞では効果が限定的であり、その場合に血管内治療が検討される。血栓吸引デバイスは複数使用可能となっている。脳梗塞急性期治療について、アルテプラーゼ、エダラボン、アルガトロバン、オザグレル、ヘパリン、ワルファリン、新規抗凝固薬、抗血小板薬について、各病型ごとの適応について概説。

心房細動の罹患率が高くなり、心原性脳塞栓症患者が増加している。初発から、寝たきり、死亡になることもあり「Knock out 型脳卒中」と言われている。心房細動を積極的に発見し、一次予防に繋げることが肝要である。これまでは、ワルファリンであったが新規凝固薬を使用する場面が増えている。脳梗塞急性期での使用、塞栓源不明の脳塞栓症（ESUS）での使用が今後の課題である。

頸動脈狭窄症においては、症候性で径狭窄率50％以上であれば手術考慮、無症候性で80％以上の場合、狭窄進行、予備能低下、無症候性梗塞、プラーク性状などの因子を総合的に評価、CEAリスクあればCAS、ソフトプラーク、屈曲・蛇行はCASリスク、年齢よりも冠動脈疾患の有無、プラーク診断、アクセス評価などが重要である。頸動脈狭窄患者には半数以上に冠動脈疾患を合併し、多くが無症候性で重症（主幹部もしくは三枝病変）であるので、積極的検索が必要である。

脳卒中治療ガイドライン2015が6月下旬に刊行予定である。脳梗塞・TIAでの改訂のポイントは、以下の通りである。

・rt･PA静注療法の治療可能時間が延長され､発症から**4.5時間以内**のrt･PA静注療法を**グレードA**として推奨した。
・**抗血小板薬2剤併用**は、発症早期の非心原性脳塞栓症または一過性脳虚血発作（TIA）の治療法として推奨項目に追加した。
・**NVAF患者への選択的トロンビン阻害薬、第Xa因子阻害薬**の経口投与は、ワルファリンと同等もしくはそれ以上の脳梗塞、全身性塞栓症の抑制効果があるとした。
・慢性期の抗血小板療法について、**シロスタゾール**の推奨レベルをアスピリン、クロピドグレルと同じグレードAとした。
・**脳梗塞・TIA患者の再発予防におけるNOACの役割**は、まだ十分なエビデンスはないものの、ワルファリンをしのぐ有効性、安全性が期待されるとした。

また、大動脈解離を合併する脳梗塞ではアルテプラーゼ静注療法は禁忌である（グレードD）。

・急性大動脈解離の**6～32％に脳梗塞**が合併。胸痛や背部痛のない大動脈解離は5～15％に認められるが、**神経学的症候を呈する例では10～55％**にもおよぶため注意が必要。
・大動脈解離による脳梗塞は、解離腔の頸動脈への波

PLOS | ONE

RESEARCH ARTICLE

Relationship between Eating Disturbance and Dementia Severity in Patients with Alzheimer's Disease

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Data Availability Statement: Data are available from Nozaki Hospital Data Access/ Ethics Committee for researchers who meet the criteria for access to confidential data. Data from Nozaki Hospital is managed by Kumamoto University. The address and telephone number of Nozaki Hospital for data requests are in the manuscript.

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Abstract

Background

Eating is one of the most important daily activities in managing patients with dementia. Although various eating disturbance occur as dementia progresses, to our knowledge, most of the studies focused on a part of eating disturbance such as swallowing and appetite. There have been few comprehensive studies including eating habits and food preference in patients with Alzheimer's disease (AD). The aims of this study were to investigate almost all eating disturbance and to examine the relationship of eating disturbance to dementia stage in AD.

Methods

A total of 220 patients with AD and 30 normal elderly (NE) subjects were recruited. Eating disturbance was assessed by a comprehensive questionnaire that had been previously validated. Potential relationships between the characteristics of eating disturbance and dementia stage as classified by the Clinical Dementia Rating (CDR) were assessed.

Results

Overall, 81.4% of patients with AD showed some eating and swallowing disturbance, whereas only 26.7% of the NE subjects had such a disturbance. Even in an early stage, patients with AD had many types of eating disturbance; "Appetite change" was shown in nearly half of the mild AD patients (49.5%). In the moderate stage, the scores of "change of eating habits and food preference" were highest, and in the severe stage "swallowing disturbance" became critical.

Conclusion

In AD, the relationship of dementia stage to eating disturbance differs according to the type of eating disturbance. The relationships between various eating disturbance and the severity of dementia should be considered.

Competing Interests: The authors have declared that no competing interests exist.

Introduction

Eating is essential to life and is one of the most important daily activities for managing patients with dementia. In caring for patients with dementia, eating takes up as large a share as help with bathing and toilet support. It is well known that various eating disturbance occur with dementia progression, including "swallowing disturbance", "change of appetite", "change of eating habits", "consumption of inedible objects" and so on. These symptoms are thought to be modulated by many factors including cognitive dysfunction, psychiatric and neurological symptoms, and decline of daily activity in individuals with dementia [1,2,3,4,5]. Despite the importance of the disturbance, there have been few systematic studies of eating disturbance compared with the other behavioral and psychological symptoms of dementia (BPSD) like hallucination and delusions.

Several studies have reported that different types of dementia present with characteristic behavioral profiles reflecting the specific brain regions affected. Furthermore, recent studies have found that the features of BPSD might be influenced by dementia stage [6,7,8]. With regard to eating and swallowing disturbance, characteristics of the symptoms in each dementia are getting clear. Patients with Alzheimer's disease (AD) sometimes suffer loss of appetite and decrease their body weight [9,10]. Some patients with vascular dementia (VaD) have pseudobulbar palsy resulting in difficulty swallowing and have a high risk of aspiration pneumonia [11,12,13,14]. Patients with dementia with Lewy bodies (DLB) have difficulty swallowing and loss of appetite [4]. Patients with frontotemporal dementia (FTD) and semantic dementia (SD) increase in appetite, come to prefer sweet and strong foods, and want to eat the same foods repeatedly [3,15]. However, most of the studies focused on a part of eating disturbance such as swallowing and appetite. There have been few comprehensive studies including eating habits and food preference in patients with AD.

The aims of this study were to investigate almost all eating disturbance and to reveal the relationship between dementia stage and characteristics of eating disturbance in patients with AD.

Materials and Methods

Ethics Statement

Before the study, a research plan was composed and put forward to the Ethics Committee of Kumamoto University School of Medicine, which was a typical comprehensive university in Japan, for reviewal and approval. All procedures for the present study strictly followed the 2011 Clinical Study Guidelines of the Ethics Committee of Kumamoto University Hospital and were approved by the Internal Review Board. After a complete description of the study was presented, informed written consent was obtained from patients and their caregivers in compliance with the research standards for human research for all participating institutions and in accordance with the Helsinki Declaration.

Subjects

This study was a prospective hospital-based cohort study. A total of 220 outpatients were selected according to the following inclusion/exclusion criteria from a consecutive series of 407 patients with dementia who attended the memory clinic of Nozaki Hospital, which is a psychiatric hospital, from April 2012 to June 2013. Among them, 60 were men and 160 women. All individuals were examined by senior neuropsychiatrists (K.K. and K.A.) using routine laboratory tests, standard neuropsychological examinations such as Mini-Mental State Examination (MMSE) [16] and brain magnetic resonance imaging (MRI) or brain computed tomography

(CT). The inclusion criterion in the present study was fulfilling the National Institute for Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association for probable AD [17]. The following patients were excluded from the current study: (1) those without a reliable informant; (2) those with developmental abnormalities, serious psychiatric diseases such as schizophrenia and major depression, or substance abuse before the onset of dementia, or significant neurologic antecedents, such as brain trauma, brain tumor, epilepsy, and inflammatory disease; (3) those complicated by an unstable physical illness, such as diabetes mellitus or malignant diseases, that would influence their eating behavior, and (4) those unable to provide informed consent.

Thirty normal elderly subjects (NE subjects) age-matched to patients were recruited from the community (12 male and 18 female). They showed normal cognitive functions (25 or above on the MMSE), normal findings in the physical and neurologic examinations, no history of psychiatric disorders, and no risk factors for cerebrovascular disease (hypertension, heart disease, and diabetes mellitus).

Measurement

The severity of dementia was rated by using the Clinical Dementia Rating (CDR) [18], of which the scores range between 0 (no cognitive decline), 0.5 (questionable dementia), 1 (mild dementia), 2 (moderate dementia) and 3 (severe dementia). In this study, CDR 0.5 and CDR 1 patients were assigned to one group during the analysis and we considered these patients as having mild dementia. Thus, we compared eating problems between four groups; "mild dementia (CDR 0.5 and 1, n = 99)", "moderate dementia (CDR 2, n = 63)", "severe dementia (CDR 3, n = 58)", and NE subjects (n = 30) groups.

To assess the characteristics of eating disturbance of AD patients, we used a comprehensive questionnaire that had been originally designed to assess eating disturbance in patients with dementia [3]. This caregiver-based questionnaire consisted of 37 items investigating the following five domains: 1) swallowing, 2) appetite, 3) food preference including sweet food preference and food fads, 4) eating habits including stereotypic eating behaviors and decline in table manners, and 5) other oral behaviors including food cramming and indiscriminate eating (Table 1). It was emphasized that a "symptom" should reflect a substantive change from a patient's premorbid state and evaluated states for the latest month. If caregivers endorsed a particular item, they were asked to rate the frequency (1 = occasionally, less than once per week; 2 = often, about once per week; 3 = frequently, several times per week but less than every day; 4 = very frequently, once or more per day or continuously); and severity (1 = mild, easily controlled; 2 = moderate, not easily controlled; 3 = marked, embarrassing or otherwise disturbing to the family), to derive a product scores (frequency × severity). The questionnaire was administered by a single rater (K.K.).

Statistical analyses

To compare the rates of each domain (swallowing, appetite, food preference, eating habits, and other oral behaviors) between the 4 groups, we used χ^2-test with Fisher's exact probability test and residual analysis using Bonferroni z-test for each comparison when an overall group difference was significant. If a patient had any symptom, we regarded positive in that domain. In the domain of "change of appetite", "loss of appetite" and "increase in appetite" were analyzed separately because of the possibility of different neural bases of the two symptoms [19,20]. Additionally, the score (frequency × severity) of each domain represented by the total score within each domain was compared between the four groups using one-way analysis of variance (ANOVA) followed by a post-hoc Sidak test. A significance level of 0.05 was set for all analyses.

Table 1. Symptoms of eating/swallowing disturbance for each domain in the questionnaire.

Swallowing disturbance	Difficulty in swallowing food
	Difficulty in swallowing liquids
	Coughing or choking when swallowing
	Taking a long time to swallow
	Placing food in mouth but not chewing it
	Chewing food but not swallowing it
Appetite change	Loss of appetite
	Increase in appetite
	Seeking out food between meals
	Overeating at meal time
	Requesting more food
	Reporting hunger
	Reporting being overfull
	Other change about appetite
	Needs to limit food
Food preference	Preferring sweet foods more than before
	Drinking more soft or sweet drinks
	Drinking more tea/coffee or water
	"Taste" in food changed in some way
	Adding more seasoning to their food
	Developing other food fads
	Hoarding foods
	Drinking more alcohol
Eating habits	Wanting to cook or eat the same food every day
	Tending to eat foods in the same order
	Wanting to eat at the same time every day
	Decline in table manners
	Eating with hands
	Other change about food preference
	Taking a long time to eat
Other eating behaviors	Tending to overfill mouth
	Chewing or sucking without trying to eat
	Eating non-edible foodstuffs
	Tending to snatch or grasp any food items
	Becoming a heavier smoker or taking up smoking
	Episodes of vomiting naturally
	Episodes of vomiting by using their fingers

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All statistical analyses were performed using IBM SPSS Statistics 21 (IBM Japan, Tokyo, Japan).

Results

Demographic variables of the four groups are summarized in Table 2. There was a significant difference in sex and age. Of the 220 AD patients, 179 (81.4%) patients showed some eating disturbance. Fig 1 shows the rates of eating disturbance in each of the four groups.

Table 3 shows the rates of each eating domain in the three patient groups and in NE subjects. Significant group differences were observed for the rates of all domains except for "loss of

Table 2. Demographics of participants.

	NE SUBJECTS (n = 30)	MILD (CDR 0.5 & 1) (n = 99)	MODERATE (CDR 2) (n = 63)	SEVERE (CDR 3) (n = 58)	All (n = 220)	P-VALUE
Male/female	12 / 18	28 / 71	15 / 48	17 / 41	60 / 160	0.458 [a]
Age (years)	80.1 ± 5.0	80.4 ± 6.4	82.1 ± 5.7	83.1 ± 5.6	81.6 ± 6.1	0.019 [b]
MMSE	27.3 ± 2.0	21.6 ± 2.8	16.7 ± 4.1	9.9 ± 5.6	17.1 ± 6.3	<0.001 [b]
Disease duration		2.5±1.9	4.7±2.8	7.1±3.8	4.3±3.4	

Notes: Values are n or mean ± SD.

NE: normal elderly; MMSE: Mini-Mental State Examination; CDR: Clinical Dementia Rating.

[a]χ^2test

[b]ANOVA

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appetite"($p = 0.153$). Z tests showed that the rates of "appetite change"($p<0.001$), "food preference"($p<0.001$) and "eating habit"($p<0.001$) domains was significantly higher in the three patient groups than in the NE subjects group. The rates of "swallowing disturbance" and "other eating behaviors" domains were significantly higher in the severe group than in any other group.

Table 4 shows the score of each eating domain. The score of all eating domains except for the "loss of appetite" increased with dementia severity, similar to the rates. It was noteworthy that the score of the "Food preference" domain in the moderate stage was significantly higher ($p = 0.002$) than in the severe one.

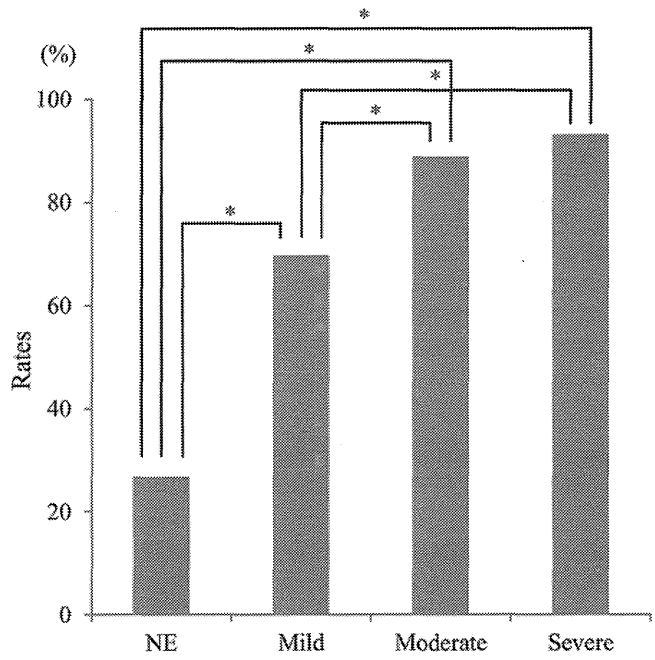

Fig 1. Rates of eating and swallowing disturbance in each stage of dementia and NE subjects. NE: normal elderly; *: An asterisk shows $p < 0.05$ with Bonfferoni correction.

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Table 3. Rates of disturbance in each domain for the subject groups.

	NE SUBJECTS (n = 30)	MILD (CDR 0.5 & 1) (n = 99)	MODERATE (CDR 2) (n = 63)	SEVERE (CDR 3) (n = 58)	P-VALUE	Z TEST WITH BONFERRONI CORRECTION
Swallowing disturbance	16.7%	22.2%	28.6%	53.4%	< 0.001	NE, Mild, Moderate < Severe
Appetite change	13.3%	49.5%	58.7%	77.6%	< 0.001	NE < Mild, Moderate, Severe; Mild < Severe
Loss of appetite	13.3%	28.3%	22.2%	34.5%	0.153	
Increase in appetite	0.0%	27.3%	39.7%	48.3%	< 0.001	NE < Mild, Moderate, Severe; Mild < Severe
Food preference	6.7%	36.4%	47.6%	46.6%	< 0.001	NE < Mild, Moderate, Severe
Eating habits	0.0%	38.4%	60.3%	58.6%	< 0.001	NE < Mild, Moderate, Severe; Mild <Moderate
Other eating behaviors	0.0%	9.1%	15.9%	37.9%	< 0.001	NE, Mild, Moderate < Severe

Note: NE: normal elderly; CDR: Clinical Dementia Rating.

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Discussion

In this study, we examined eating disturbance in a large (n = 220) sample of patients with AD. To our knowledge, this is the first study that used a single, previously validated questionnaire to evaluate eating disturbance in AD in relation to dementia severity.

The most remarkable finding was the fact that as many as 81.4% patients with AD showed some eating disturbance, whereas only 26.7% of the NE subjects had disturbance. The rates of eating disturbance, assessed by using Neuropsychiatric Inventory (NPI), in patients with AD was previously reported as 23.5% to 51.6% [8,21]. The higher rates of our study might be due to the sensitivity of our assessment tool. The large difference in rates between patients with AD and the NE subjects demonstrates the significance of eating disturbance for managing patients with AD.

Previously, it was reported that the rates of all symptoms in NPI increased along the severity of the disease, except for sleep and eating disturbance [22]. They showed that the rates of "eating disturbance" was 24.5% in moderate-severe AD, 15.2% in mild AD, 19.8% in Mild Cognitive Impairment, and 6% in controls and no significant differences were found among the groups. In the present study, "increase in appetite", "swallowing disturbance" and "other eating behaviors" increased in proportion to severity of dementia. On the other hand, the score of "food preference" and "eating habits" became highest in the moderate stage and declined

Table 4. Scores for each eating/swallowing domain in the four subject groups.

	NE SUBJECTS (n = 30)	MILD (CDR 0.5 & 1) (n = 99)	MODERATE (CDR 2) (n = 63)	SEVERE (CDR 3) (n = 58)	P-VALUE	POST HOC SIDAK TEST
Swallowing disturbance	0.17 ± 0.4	1.36 ± 6.5	2.98 ± 9.8	5.22 ± 8.8	0.007	NE, Mild < Severe
Appetite change	0.13 ± 0.4	3.24 ± 4.7	7.10 ± 12.7	5.71 ± 7.6	< 0.001	NE < Moderate, Severe; Mild < Moderate
Loss of appetite	0.13 ± 0.4	1.53 ± 3.1	1.52 ± 4.0	2.17 ± 3.9	0.069	
Increase in appetite	0.00 ± 0.0	1.73 ± 4.1	5.57 ± 12.1	3.53 ± 7.4	0.002	NE, Mild < Moderate
Food preference	0.07 ± 0.3	2.31 ± 5.3	5.10 ± 10.1	2.00 ± 3.6	0.002	NE, Mild < Moderate; Severe < Moderate
Eating habits	0.00 ± 0.0	2.30 ± 4.6	6.44 ± 9.4	4.81 ± 6.4	< 0.001	NE < Moderate, Severe; Mild < Moderate
Other eating behaviors	0.00 ± 0.0	1.34 ± 0.7	0.70 ± 2.34	1.66 ± 3.2	< 0.001	NE, Mild < Severe

Notes: Values are mean ± SD.

NE: normal elderly; CDR: Clinical Dementia Rating.

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afterward. The relationship of dementia stage should be different among the domains of eating disturbance.

Patients with AD in the mild stage have been reported to show few eating disturbance, similar to the neurologic manifestations [3,4,5,15]. However, in the present study, patients with AD had many types of eating disturbance even in an early stage. Especially, "appetite change" was shown in nearly half of the mild patients with AD (49.5%). The difference might be partially explained by sampling bias. Subjects in the previous studies were from the memory clinic in a university hospital while those in this study were from the memory clinic in a psychiatric hospital. Weight loss and low body weight have been commonly reported in AD. Furthermore, a recent longitudinal study, involving community-dwelling elderly, found that participants with incident dementia or MCI had accelerated weight loss from as early as 6 years before diagnosis of AD [23]. In the present study the rates of "loss of appetite" was about twice as high in each severity group of AD as in the NE subjects group although the difference between patients with AD and NE subjects did not reach the significance level. We should consider the importance of "loss of appetite" in all severity stages of AD patients. It was interesting that two conflicting eating symptoms, "increase in appetite" and "loss of appetite", were observed in approximately the same number of patients with mild AD. Although fundamental pathophysiological mechanism for "appetite change" is unclear, this condition might reflect different neuropsychological and neuropsychiatric symptoms associated with AD. Appetite loss is well known as being a main symptom of depression and as many as 68.0% patients with AD were reported to have some depressive symptoms [24]. There was a possibility that depression might be concerned about "loss of appetite". On the other hand, "increase in appetite" might reflect the behavior of having a meal in a repetitive manner because of severe memory impairment. We need to do a longitudinal study for revealing whether a case of "loss of appetite" convers to a case of "increase in appetite".

In the mild stage, over one-third of patients showed changes in "food preference" and "eating habits". The score of "food preference", "eating habits", "appetite change" and "increase in appetite" became highest in the moderate stage and declined afterward even if some are not statistically significant. It may reflect some sort of 'burnout' leading to increased behavioral apathy. These eating behaviors may require a certain level of functional ability in patients with AD. The details of "food preference" were changing to prefer sweet foods and candies, and adding strong flavor to their dishes using soy sauces. It is not clear yet whether the gustatory function is impaired in patients with AD. Previous research reported that the gustatory function of patients with AD was not impaired [25,26]. On the other hand, Steinbach et al. (2010) investigated the gustatory recognition threshold in mild AD patients, MCI patients, and normal elderly subjects using an actual taste test, and they showed the impairment of gustatory recognition for all four basic tastes in the patient group, even at the MCI stage [27]. Although the present study did not make a direct examination of gustatory function of patients with AD, our results may indicate the possible presence of gustatory dysfunction in mild AD in an indirect fashion.

"Swallowing disturbance" was critical in the severe stage AD. Humbert et al. investigated the relationship between swallowing disturbance and severity of dementia, and they found that there were a few patients with AD who showed swallowing disturbance in their mild or moderate stage, and more patients presented with this symptom as dementia progressed [28]. In the current study, approximately half of the patients in the severe stage had developed swallowing disturbance, which was lower than we expected. We thought that this might be due to the fact that some of our patients with swallowing disturbance had already been taken care by professional caregivers or the nursing staff in a daycare unit using a thick liquid and minced food.

There are a few methodological issues that should be taken into consideration when interpreting our results. First, the diagnosis relied solely on clinical basis without histopathologic confirmation, with inevitably some uncertainty about the rate of misclassification. Secondly, we did not consider the influence of other neuropsychiatric symptoms and neuropsychotropic drugs such as neuroleptics, SSRIs, SNRIs, and cholinesterase inhibitors. These symptoms and drugs might have some effects of changing appetite and swallowing disturbance. Thirdly, due to the cross-sectional study design, the relationship between the severity of dementia and eating disturbance could only be hypothesized. It remains an open question whether "loss of appetite" and "increase in appetite" shift relative to each other in the same patient with disease progression or if the two conditions are shown in different patients. Longitudinal research may offer additional information on the development and course of eating disturbance in patients with AD.

Conclusion

The present findings indicated the importance of paying attention to various eating disturbance corresponding to the severity of dementia. With foresight, caregivers can handle eating disturbance in AD when the characteristics and longitudinal changes are revealed.

Supporting Information

S1 Table. Data of this study including values and statistical results.
(XLSX)

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Author Contributions

Conceived and designed the experiments: MI. Performed the experiments: KK. Analyzed the data: KK. Wrote the paper: KK MI MH RF. Collected the data: KA HT.

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ORIGINAL ARTICLE

Relationship between dementia severity and behavioural and psychological symptoms in early-onset Alzheimer's disease

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Abstract

Background: The features of behavioural and psychological symptoms of dementia (BPSD) are influenced by dementia stage. In early-onset Alzheimer's disease (EOAD), the association between BPSD and dementia stage remains unclear because of the difficulty of recruiting subjects with a wide range of disease severity. We used a combination of community-based and hospital-based approaches to investigate the relationship between dementia severity and BPSD in EOAD patients.

Methods: Sixty-three consecutive EOAD outpatients and 29 EOAD patients from a community-based survey were divided into three dementia severity groups according to the Clinical Dementia Rating scale (CDR): mild (CDR 0.5–1, $n = 55$), moderate (CDR 2, $n = 17$), and severe (CDR 3, $n = 20$). BPSD were rated using the Neuropsychiatric Inventory.

Results: Scores of the Neuropsychiatric Inventory subscales agitation, euphoria, apathy, disinhibition, irritability, and aberrant motor behaviour increased significantly with increased dementia severity. Hallucinations were greater in the moderate group than in the mild group. For delusions, depression, and anxiety, no significant differences were observed among the three severity groups.

Conclusions: The pattern of apathy, agitation, disinhibition, irritability, and aberrant motor behaviour worsening with severity progression in EOAD is similar to the pattern in late-onset Alzheimer's disease. In contrast, hallucinations, depression, and anxiety showed different patterns in EOAD.

Key words: *Alzheimer's disease, behavioural and psychological symptoms (BPSD), early-onset, Neuropsychiatric Inventory (NPI), severity of dementia.*

INTRODUCTION

Alzheimer's disease (AD) is the most frequent diagnosis in dementia. AD is divided into early-onset (EOAD) and late-onset (LOAD) according to whether the onset is before or after 65 years of age. Previous reports based on large clinicopathologic studies have shown that the pathologies of EOAD and LOAD are not qualitatively different.[1,2] However, several studies have revealed distinct neurocognitive and neuroimaging features in EOAD patients. For example, language problems and visuospatial dysfunction are common in EOAD,[3] and in a neuroimaging study, EOAD patients exhibited a more severe reduction in grey matter in the bilateral parietal and posterior cingulate cortices and precuneus region.[4] These findings suggest it may be necessary to consider EOAD and LOAD as separate diseases clinically.

'Behavioural and psychological symptoms of dementia' (BPSD) is a descriptive term that encompasses a heterogeneous group of non-cognitive symptoms and behaviours occurring in patients with dementia.[5] The development of BPSD is associated with more rapid cognitive decline,[6] greater impairment in activities of daily living,[7] lower quality of life for patients and caregivers,[8] and earlier institutionalization.[9] Different types of dementia present with characteristic behavioural profiles that reflect specific brain regions affected and neurotransmitter

abnormalities. Recent studies have suggested the features of BPSD are influenced by the dementia stage.[10–19] Although a relationship between dementia severity and BPSD has been reported in LOAD patients,[10,11,13,14,19] there has been no similar study in EOAD. We think that EOAD patients may have a characteristic pattern of BPSD as dementia severity progresses, and comprehending the pattern is important to direct treatment and to plan care and support for patients and their caregivers. It is hard to recruit a sufficient number of EOAD patients for valid statistical analysis. Additionally, because many patients seen in the memory clinic have mild dementia, it is difficult to recruit a wide range of dementia severity in hospital-based studies. In the present study, we solved these problems by combining a hospital-based study with a community-based study, and we investigated the relationship between dementia severity and BPSD in EOAD patients.

METHODS

Subjects

All procedures followed the Clinical Study Guidelines of the Ethics Committee of Kumamoto University Hospital and were approved by the internal review board. After receiving a complete description of all procedures for the present study, all patients or their caregivers, if surrogate consent was needed, provided written informed consent.

Sixty-three patients with EOAD who consecutively visited Kumamoto University Hospital between April 2007 and May 2013 comprised the hospital outpatients in our study. Patients underwent general physical, neurological, and neuropsychological examinations, including the Mini-Mental State Examination (MMSE).[20] All underwent structural neuroimaging with magnetic resonance imaging of the brain and routine laboratory tests. In addition to these 63 hospital outpatients, we included 29 EOAD patients from our community-based survey on the prevalence of early onset dementia.[21] This study was conducted in the same catchment area as our university hospital in 2008. We visited these EOAD patients at home, in the hospital, or in the nursing home and examined them using the same procedure as used on the outpatients. We referred to blood work and structural neuroimaging with computed tomography or magnetic resonance imaging of the brain that had been performed by their regular doctors. The purpose of combining these two patient groups was to investigate BPSD of EOAD over a range of disease severity.

Patients who satisfied the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association diagnostic criteria for probable AD were put into the EOAD group if they were under 65 years old at examination.[22] We decided to classify subjects by age at first assessment to avoid the possibility that inaccurate medical histories would confound the age of onset.[23] Patients were excluded from the study if they had developmental abnormalities, serious psychiatric disease, a history of substance abuse, or significant neurologic antecedents, such as brain trauma, brain tumour, epilepsy, and inflammatory disease. Patients without a reliable informant were also excluded.

Assessments and measures

Neuropsychiatrists who examined patients rated the severity of dementia using the Clinical Dementia Rating (CDR).[24] We classified the patients into three groups according to the CDR: mild dementia (CDR 0.5–1, $n = 55$), moderate dementia (CDR 2, $n = 17$), and severe dementia (CDR 3, $n = 20$).

We assessed patients' comprehensive BPSD through a structured caregiver interview that employed a Japanese version of the Neuropsychiatric Inventory (NPI).[25,26] The NPI was used to rate 10 symptoms on the basis of a patient's condition during the month before the interview: the symptoms were delusions, hallucinations, agitation, depression, anxiety, euphoria, apathy, disinhibition, irritability, and aberrant motor behaviour (AMB). According to the criteria-based rating scheme, the severity of each manifestation was classified into four grades (from 1 to 3; 0 if absent), and the frequency of each manifestation was also classified into five grades (from 1 to 4; 0 if absent). The NPI score (severity × frequency) was calculated for each manifestation (range of possible scores: 0–12). The presence of a symptom was expressed as an NPI subset score >0. The maximum total score on the NPI for the 10 manifestations is 120.

The CDR and NPI assessments were performed within 1 month of the first visit or on the day we visited patients in their home.

Statistical analysis

Demographic and clinical variables, NPI total score, and the score of each individual NPI domain were evaluated between groups with χ^2 analysis, one-way ANOVA, and the post-hoc Tukey test. For all analyses, a *P*-value <0.05 was regarded as statistically significant. Statistical operations were performed with SPSS for Windows, version 17.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

The overall sample's mean age ± SD at examination was 59.0 ± 3.8 years, and the mean MMSE score ± SD was 13.4 ± 8.8. The 63 participants in the hospital-based study included 50 mild cases, 12 moderate cases, and 1 severe case. The 29 participants in the population-based study included 5 mild cases, 5 moderate cases, and 19 severe cases. The majority of participants in this study received in-home care (n = 81). Seven subjects received hospital treatment, and four received nursing home care.

No significant differences were found in age, sex ratio, and educational level among the three severity groups; these demographic variables are shown in Table 1. Dementia severity was significantly associated with disease duration. The MMSE score showed a significant decrease with dementia severity.

Table 2 shows the prevalence of neuropsychiatric symptoms according to dementia severity group. Apathy was the most common behaviour, which was exhibited by 82.6% of all patients, followed by depression (39.1%), anxiety (35.9%), and irritability (33.7%). Disinhibition was the least common, developed by only 5% of all EOAD patients.

Figure 1 shows the mean NPI total scores in the three groups. The total NPI score increased across each group with significant differences between the mild and moderate dementia groups ($P < 0.05$) and between the mild and severe groups ($P < 0.01$).

The NPI subscale scores of agitation, euphoria, apathy, disinhibition, irritability, and AMB increased with dementia severity (Table 3). Significant differences were found between the severe group and both the mild and moderate groups in terms of agitation ($P < 0.01$), euphoria ($P < 0.05$), disinhibition ($P < 0.05$), and irritability ($P < 0.05$); these subscales did not differ between the mild and moderate groups. Severity progression increased apathy ($P < 0.01$), with significant differences between all groups. The severe group had significantly greater AMB ($P < 0.01$) than the mild group. There were more hallucinations in the moderate group than in the mild group ($P < 0.05$), with no further increase in the severe group. Three NPI

Table 1 Patient demographics and clinical characteristics

	Mild (n = 55)	Moderate (n = 17)	Severe (n = 20)	*P*-value
Age at examination, mean ± SD (year)	58.8 ± 4.1	58.8 ± 3.7	59.7 ± 3.1	0.69†
Sex (men/women)	19/36	6/11	6/14	0.95‡
Education, mean ± SD (year)	12.5 ± 2.3	11.3 ± 2.9	11.7 ± 2.3	0.16†
Duration, mean ± SD (year)	2.7 ± 1.7	4.7 ± 2.1	9.4 ± 4.4	<0.001†
MMSE, mean ± SD	19.2 ± 4.5	9.4 ± 5.6	0.8 ± 1.9	<0.001†

†One-way ANOVA. ‡χ^2 test. MMSE, Mini-Mental State Examination.

Table 2 Prevalence of neuropsychiatric symptoms in each stage of dementia

NPI item	Total (%) (n = 92)	Mild (%) (n = 55)	Moderate (%) (n = 17)	Severe (%) (n = 20)
Delusions	14.1	12.7	17.6	15.0
Hallucinations	8.7	1.8	23.5	15.0
Agitation	26.1	20.0	23.5	45.0
Depression	39.1	41.8	47.1	25.0
Anxiety	35.9	40.0	41.2	20.0
Euphoria	8.7	5.5	0	25.0
Apathy	82.6	76.4	82.4	100
Disinhibition	5.4	1.8	0	20.0
Irritability	33.7	32.7	29.4	40.0
AMB	26.1	16.4	41.2	40.0

AMB, aberrant motor behaviour; NPI, Neuropsychiatric Inventory.

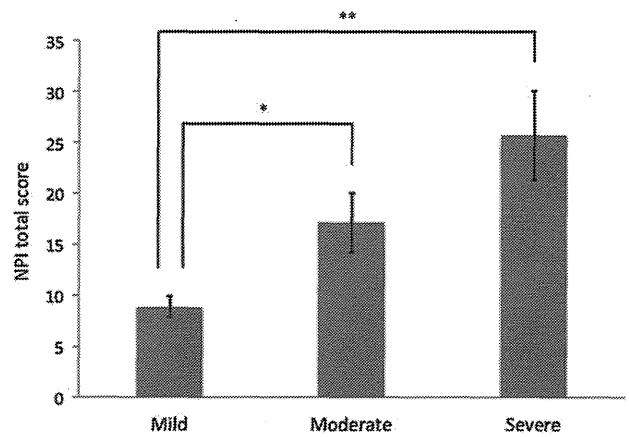

Figure 1 Mean Neuropsychiatric Inventory (NPI) total score by dementia group. Error bars represent standard error of the mean. *P < 0.05, **P < 0.01 by a multiple comparison using Tukey test.

Table 3 Mean scores for each NPI subscale by dementia severity group

NPI item	Dementia severity				
	Mild (n = 55)	Moderate (n = 17)	Severe (n = 20)	P-value	Pairwise comparisons†
Delusions	0.33 ± 1.04	1.59 ± 3.99	0.90 ± 2.79	0.127	
Hallucinations	0.02 ± 0.14	1.47 ± 3.39	0.90 ± 2.77	0.017	Mild < moderate
Agitation	0.67 ± 1.51	0.76 ± 1.68	3.60 ± 4.94	<0.001	Mild, moderate < severe
Depression	1.18 ± 1.88	1.47 ± 3.00	0.55 ± 1.10	0.34	
Anxiety	1.40 ± 2.31	2.00 ± 3.39	0.95 ± 2.14	0.45	
Euphoria	0.13 ± 0.61	0	1.15 ± 2.83	0.013	Mild, moderate < severe
Apathy	3.36 ± 3.19	6.29 ± 4.15	10.20 ± 2.75	<0.001	Mild < moderate < severe
Disinhibition	0.02 ± 0.14	0	1.45 ± 3.33	0.002	Mild, moderate < severe
Irritability	1.00 ± 1.81	0.65 ± 1.22	2.70 ± 4.05	0.014	Mild, moderate < severe
AMB	0.75 ± 2.08	2.88 ± 4.00	3.65 ± 4.89	0.001	Mild < severe

Data are shown as mean ± SD. †Post-hoc Tukey test. AMB, aberrant motor behaviour; NPI, Neuropsychiatric Inventory.

subscale scores (delusions, depression, and anxiety) showed no significant difference in the three severity groups.

DISCUSSION

To our knowledge, this is the first study attempting to clarify the relationship between dementia severity and neuropsychiatric symptoms in EOAD patients. It is difficult to recruit many outpatients in the severe stage of dementia for a cross-sectional study for any degenerative disease, including EOAD. Longitudinal studies require a time commitment from patients and their caregivers, and longitudinal studies for degenerative diseases often suffer from attrition as participants drop out. To address these issues, we performed a cross-sectional study but combined patients who were recruited from a community-based study with outpatients recruited from a memory clinic. Therefore, we were able to compare EOAD patients with a wide range of dementia severity. We think this method is very useful for cross-sectional studies researching uncommon and slowly progressive diseases if the same diagnostic and assessment methods are available in both hospital-based and community-based studies.

There have been two previous hospital-based studies on the prevalence of neuropsychiatric symptoms in EOAD patients that used NPI, and one of them used the same method of assessing NPI symptom criteria (an NPI subset score >0) as our study. [23] Our results were very similar to their findings except for the symptoms of apathy (82.6% vs 56.5%) and irritability (33.7% vs 19.6%). These differences may be due to our inclusion of more severe patients (mean MMSE score: 13.4 vs 17.4).

In the present study, agitation, apathy, disinhibition, irritability, and AMB became worse with increased dementia severity. This pattern was consistently observed in previous studies of LOAD patients.[10,13,19] In AD, agitation and AMB have been associated with a greater neurofibrillary tangle burden in the orbitalfrontal cortex, and apathy has been associated with the anterior cingulate area.[27] Aggravation of these symptoms might be associated directly with advancing brain damage around these areas, and therefore, this pattern might be common in both EOAD and LOAD patients.

Hallucinations were higher in the moderate group than in either the mild or severe groups in the current study. Several studies of LOAD patients have reported that hallucinations become worse with dementia severity.[13,14,19] This may reflect a difference in the pattern of cortical dysfunction. Neuroimaging investigations revealed that patients with EOAD exhibited a more severe reduction in grey matter in the bilateral parietal and posterior cingulate cortices and precuneus region than those with LOAD.[4] Therefore, hallucinations in EOAD might appear in a milder stage than in LOAD, reflecting a difference in the pattern of brain damage.

Depression and anxiety had a relatively high frequency and showed no significant difference among the three groups. These two symptoms have been grouped together by several factor analysis studies on AD and also showed a similar pattern in our study.[28–30] Both symptoms appeared in the mild or moderate stage and decreased in the severe stage. In AD patients, mainly LOAD, depression has been reported to be more severe in the moderate stage.[12,16] We think

this discrepancy might be due to a high occurrence of depression in the mild group of EOAD patients. There are many EOAD patients who have a role in society or family at the time of disease onset, potentially creating a greater risk of poor social adjustment from an early stage. Depression and anxiety are likely influenced by both psychosocial factors and advancing brain damage in EOAD.

The strength of the present study is that we examined BPSD among EOAD patients with a wide range of dementia severity. However, several methodological issues limit the interpretation of the results of this study. First, the homogeneity of this cohort is open to question given the combination of a hospital-based study with a community-based study, although all subjects underwent the same diagnostic and assessment procedures. Second, we did not investigate medication use. Taking anti-dementia and/or psychotropic agents could affect the results of the study. Third, the cross-sectional study design may not have been optimal because behavioural disturbances can fluctuate and may not be present at every examination.[31] A longitudinal study may offer additional information on the course of BPSD in EOAD patients. Despite these limitations, we believe that our findings may be useful for the management and care of EOAD patients in their home or in institutions.

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