2）認知症（DSM-5）

3．前頭側頭型認知症（DSM-5）

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Ⅰ．疾患の概念と診断

前頭側頭葉変性症（frontotemporal lobar degeneration：FTLD）[40]は，著明な精神症状や行動障害，言語障害を主徴とし，前頭葉，前部側頭葉に病変の主座を有する，古典的ピック病をプロトタイプとした変性性認知症を包括した疾患概念である。しかし，FTLDという用語は，神経病理学的検討や分子生物学的分類に限って用いられるようになってきており，臨床的には前頭側頭型認知症（frontotemporal dementia：FTD）が包括概念として用いられつつある。そして，臨床サブタイプとして，行動障害が前景に立つ行動障害型前頭側頭型認知症（behavioral variant frontotemporal dementia：bvFTD），言語障害型前頭側頭型認知症（language variant frontotemporal dementia：lvFTD）などに分類される。

DSM-5におけるFTDも上記の包括的概念で使用されており，DSM-Ⅳにおける「ピック病による認知症」に対応するが，DSM-5で大きく変わった章の1つである神経認知障害群のなかでも最も大きく変化した項目の1つである[2]。近年のこの領域の著しい研究成果によって内容はほぼ一新されているといっても過言ではない。臨床亜型として行動障害型と言語障害型に分類されたが，これらの概念ならびに診断基準は最近相次いで出版されたbvFTD[45]ならびに原発性進行性失語（primary progressive aphasia：PPA）[18]の国際診断基準に大きく影響を受けていることは間違いない。

診断を下すためには「A．認知症の基準を満たす」，「B．その障害は潜行性に発症し緩徐に進行する」すなわち変性疾患があることが要件である。そして，基準Cとして行動障害型あるいは言語障害型のいずれかの基準を満たす必要があるが，両方の特徴を呈している例も多い。言語障害型は前述したPPAの診断基準にならい3つの言語障害型（意味型，失文法／非流暢性型，ロゴペニック型）に分類し，失語を正確に把握する必要がある。また確実な（probable）診断を下すには，家族歴または遺伝子検査による遺伝子変異の証明，もしくは神経画像による前頭葉および／または側頭葉の突出した関与の証拠が必要とされている。詳細はDSM-5を参照されたい。

診断の基本になる主要な特徴をDSM-5の診断基準に沿って紹介する。

1．行動の脱抑制

早期からの脱抑制は，bvFTDの重要な特徴で，アルツハイマー病など他の認知症との鑑別にも有用である[4, 7, 12]。他人になれなれしく接近したり触ったりキスしたりする，言葉の暴力や身体的暴力，公衆の面前で裸になったり放尿したりする，不適切な性的行動などである。

2．アパシーまたは無気力

アパシー／無気力はbvFTDのほぼ共通した初発症状であり，他の認知症に比べて重度でかつ広範である[4, 9, 50]。「アパシー」は，熱意，意欲，あるいは興味の喪失と定義される。ものぐさな態度や自発性の欠如といった症状で現れるかもしれな

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い。重要な，あるいは過去には意義のあった活動（たとえば，仕事や趣味）を開始することができず，中止してしまう。無気力は，行動を開始することが少なくなることであり，たとえば歯磨きを開始したり終了したりするにも特別な指示を必要とする。

3．思いやりの欠如または共感の欠如

他人の感情表出を理解したり他人の体験を想像することができない。初期の頃からよくみられる特徴であり，無関心や社会参加の全般的な減少をしばしば伴っている。この症状は，アルツハイマー病との鑑別に特に有用である[34,44]。剖検例によるFTDC診断基準の感度と特異度の検討では，FTDに特異度が高い症状とされている[20]。日常生活では，感情を傷つけるコメントや他人の痛みや苦痛を無視することなど，他人の感情に対する理解の欠如，あるいは無関心といった形で現れる。情動的な無関心，冷たさ，アイコンタクトの欠如などを伴う社会参加の全般的低下が認められることもある。

4．保続的，常同的または強迫的／儀式的行動

繰り返し机などを軽く叩く，拍手する，あるいは膝をこする，体をゆすり続ける，鼻歌を歌い続けるなどの反復動作のほか，儀式的に数を数えたり掃除したりする，物を集めたりため込んだりする，用事もないのに繰り返しトイレに行く，決まった道を散歩するなど複雑な，強迫的な行動が含まれる。これらの行動は，他の原発性認知症との鑑別に有用である[4,7,50]。

5．口唇傾向および食行動の変化

食事や食行動の変化もアルツハイマー病との鑑別には有用である[3,4,7,24]。通常炭水化物，特に甘いものへの渇望あるいは食べ物へのこだわり（強固な，常同的な，あるいは風変わりな食物嗜好）として出現する。過食や飲酒または喫煙量の増加もみられ，極端な場合は「何でも口に入れる，食べられないものを摂取する」といった口唇傾向を認める。

6．神経心理学的プロフィール

実行機能／生産的な機能の障害とそれに比べて保たれている記憶や視空間機能とが特徴である[19,55]。早期の段階では，認知機能の低下は行動障害に比べると目立たず，正規の認知機能検査ではあまり低下を認めないこともあるが，上記の剖検例での検討では，感度が高い症状として報告されている[20]。

7．診断マーカー

行動障害型と3つの言語障害型（意味型，失文法／非流暢性型，ロゴペニック型）はおのおの特徴的な神経画像所見を示し，一部は遺伝子異常も明らかになっている。CTないしMRIで特徴的な萎縮パターンを認める[28,31,35,49,54]。行動障害型では，両側前頭葉と側頭葉前方部に萎縮を認める。言語障害型のうち意味型は，側頭葉中・下部と前方部の両側性萎縮を呈するが，左右差があり通常は左側の萎縮がより強い。失文法／非流暢性型は，左側優位の前頭葉後方-島回の萎縮と関連している。ロゴペニック型は，左優位のシルビウス裂後方ないし頭頂葉の萎縮と関連している。機能画像では，形態画像ではまだ異常を認めない早期の段階から，対応する部位の血流低下ないし代謝低下を認める[28,35,49]。

Ⅱ．治療の方針

1．全体的な治療方針

FTDでは脱抑制や常同行動などの行動変化で家族や介護者が対処に困ることが多く，認知症の行動・心理症状（BPSD）が治療対象となる。

2．薬物療法の占める意義（エビデンスの強さの程度）

FTDにおいては十分に実証され保険適用のある薬物はない。

3．非薬物療法の意義

保険適用のある薬物療法がない現時点においては，非薬物療法と環境調整が治療の中心となる。FTD特有の常同行動や被影響性の亢進を利用したルーティーン化療法[52]や，危険な行動の常同化

表1　抗うつ薬に関する報告（Riedl, et al., 2014.[47]より引用，一部改変）

薬剤	報告者	実施方法	人数	治療期間	BPSD	認知機能
paroxetine（20mg），piracetam（1,200mg）	Moretti[38]	無作為化，オープン	16	14ヵ月	パロキセチン群で行動障害が改善	不変
paroxetine（40mg）	Deakin[13]	プラセボ対照無作為化二重盲検	10	6週	有意差なし	一部低下
sertraline（50-100mg）	Mendez[33]	オープン	8	6ヵ月	常同行動が改善	評価せず
trazodone（300mg）	Lebert[30]	プラセボ対照無作為化二重盲検	26	12週	易刺激性，焦燥，抑うつ，食行動異常が改善	有意差なし
fluvoxamine（50-150mg）	Ikeda[25]	オープン	15	12週	特に常同行動が改善	不変
citalopram（40mg）	Herrmann[21]	オープン	15	6週	改善	評価せず
moclobemide（300-600mg）	Adler[1]	オープン	6	4週	やや改善	不変

に対する短期入院治療[23]が行動異常や介護負担の減少に有効であるとの報告があり，薬物療法を開始する以前に，もしくは並行して試みる価値はある。しかしながらこれらの報告はいずれもオープン試験であり，FTDに対する非薬物療法において大規模な無作為化試験の報告はない。これについては患者数が少ないことや専門家以外では診断が困難であること，評価尺度が乏しいこと，さらに介護環境の統制が難しいことが理由として考察されている[51]。

4．薬物療法開始の判断とタイミング

FTDでは疾患早期からBPSDが前景に立つことが多く，それらの行動上の破綻は家庭での介護のみならず，入院や施設内ケアの場面においてもはなはだしい困難をもたらす。そのためBPSDへの介入は早期からが望ましいが，前述のごとく十分に有効性が実証された薬物がない現時点において，薬物療法の開始についてはそのリスクとベネフィットについて家族と十分に検討した上でなされる必要がある。

Ⅲ．薬物の選択と投与法

1．第1選択の薬物選択

FTDにおける神経伝達機能については，アルツハイマー病やレビー小体型認知症において機能低下がみられるコリン作動系は比較的保たれているとされる[22, 43]。一方で，セロトニン作動系の機能低下については強いエビデンスがあり，縫線核におけるセロトニン1A・2A受容体の減少と神経細胞脱落が示されている[22]。これらの知見に基づいて，抗うつ薬，特にSSRIやドパミン作動性の薬物を使用した研究が報告されているが，コリンエステラーゼ阻害薬やグルタミン酸受容体遮断薬といったアルツハイマー病の治療薬を使用した研究もまた報告されている。これらのうち，現時点で最初に使用が考慮される抗うつ薬について，代表的な報告を表1に示す。SSRIをはじめとした抗うつ薬がFTDにおける脱抑制やアパシー，常同行動，性的逸脱行動，口唇傾向に対して効果を有する一定のエビデンスはあり[22, 32]，近年，日本神経学会はFTDの行動障害を改善する目的でのSSRIの使用を推奨グレードC1[41]，また英国精神薬理学協会は推奨グレードBと定めている[42]。

2．第2選択以降の薬物療法

FTDにおいてドパミン作動系の機能低下も示されており[42]，被殻・尾状核におけるドパミン代謝産物の減少，シナプス前部のドパミン受容体の減少[48]が報告されている。ドパミン作動系の薬剤を使用した研究はいくつか存在するが，いずれも症例数が限られており，エビデンスとしては弱い。2011年にFTD 20例にオキシトシンを投与しBPSD

表2 アルツハイマー型認知症治療薬に関する報告（Riedl, et al., 2014.[47]より引用，一部改変）

薬剤	報告者	実施方法	人数	治療期間	BPSD	認知機能
rivastigmine（3-9mg）	Moretti[39]	オープン	20	12ヵ月	改善	不変
donepezil（5-10mg）	Mendez[36]	無作為化，オープン	24	6ヵ月	脱抑制，強迫症状が悪化	不変
donepezil（10mg），rivastigmine（6-12mg）	Lampl[29]	無作為化比較	9	6ヵ月	評価せず	改善
galantamine（16 or 24mg）	Kertesz[27]	オープン，プラセボ対照無作為化二重盲検	36	18週，8週	有意差なし	有意差なし
memantine（20mg）	Diehl-Schmid[14]	オープン	16	6ヵ月	不変	悪化
memantine（20mg）	Vercelletto[53]	プラセボ対照二重盲検	49	52週	やや改善	有意差なし
memantine（20mg）	Chow[10]	オープン	16	7，8週	不変	不変
memantine（20mg）	Boxer[6]	プラセボ対照無作為化二重盲検	76	26週	有意差なし	有意差なし

が改善したとの報告があり[26]，さらなる治験が進行中である。

コリン作動系が比較的保たれる[22, 43]FTDにおいて，アルツハイマー病の治療薬であるコリンエステラーゼ阻害薬による恩恵は期待できないにもかかわらず，表2に示す通り多くの報告がある。総合的にみるとコリンエステラーゼ阻害薬はFTD患者の認知機能，精神症状を改善しない。グルタミン酸受容体拮抗薬であるmemantineは，いくつかのオープン試験においてBPSDへの効果について結果が分かれ[10, 14, 53]，有効か否かの検証が待たれていた。しかし最近の二重盲検RCTにおいてその有効性は否定されている[6]。

3．難治例への対応（適応外使用についての記載を含む）

抗精神病薬，特に非定型抗精神病薬は認知症の背景疾患に関わらず，脱抑制や興奮，精神病症状など激しいBPSDに使用されている[17]。FTD患者へのcontrolled studyは存在せず，有効性を示唆する報告がいくつかあるのみである[11, 16, 38]。認知症を有する高齢者での服用は死亡率の増加（1.6～1.7倍）を引き起こすという研究結果があり[15]，使用にあたっては利益と危険性とを慎重に見極めることが必要である[8]。また，他の認知症同様に錐体外路症状，糖尿病，心血管系イベントなどを考慮しながら最小限，短期間の使用にとどめることが望ましい。

Ⅳ．患者と家族への説明

FTDへの薬物療法はすべて適応外使用であり，そのことを確実に伝えるとともに使用にあたっては家族と十分に検討する必要がある。FTD患者の介護負担はアルツハイマー病など他の認知症と比較して非常に大きいことが明らかになっており[5, 37, 46]，また機能障害の程度よりBPSDのほうが介護負担と相関が強いとされる[5]。薬物療法によるBPSDの改善は，介護負担の軽減が期待される一方で，処方内容・量によっては患者本人の意思表明をも妨げる恐れがある。過剰な薬物療法を避けるためには前述の非薬物療法，環境調整を試みながら，家族に病気について正確な情報を提供し，理解してもらうことが治療上必要となる。なお，平成27年7月1日よりbvFTDと意味性認知症すなわち意味性言語障害型が国の難病対策の指定難病に加わった。医療費助成を受けるには発症が65歳以下であること，重症度が中等度以上であることなどの要件があるが，経済的負担の軽減のために適切に家族に情報提供を行う必要がある。

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アルツハイマー病のBPSDとその対応

田中 響，橋本 衛，池田 学

抄録

認知症に伴う行動・心理症状（BPSD）は，患者のQOLを低下させ介護者の負担を増大させる一方で，適切な対応により改善が期待できる症状である．記憶障害や見当識障害などの中核症状を基礎に，ストレスや疎外感といった心理因子，さらにそれに影響する環境因子などが加わった結果が，BPSDとして表出されると考えられている．BPSDの治療は，患者の心理機序に沿ったケアや環境調整などの非薬物療法を優先し，薬物療法は効果が期待される症状にのみ行うことが推奨される．本稿では，アルツハイマー病におけるBPSDの特徴，その発現機序および対応法について概説した．

Key words：アルツハイマー病，BPSD，治療，非定型抗精神病薬

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はじめに

認知症の行動・心理症状（behavioral and psychological symptoms of dementia；BPSD）は患者の生活の質（quality of life；QOL）を低下させるだけでなく，介護者の負担も増大させる[43]．さらにはBPSDの悪化は認知機能障害の進行[41]，早期の入院・入所[9]，そして医療や介護費用の増大[16]と関連するなどの知見も集積されており，BPSDを適切に治療することは，認知症診療においてきわめて重要である．

本稿では，われわれ認知症医療に携わる医師が日常的に接する機会の最も多い認知症疾患であるアルツハイマー病（Alzheimer's disease；AD）のBPSDと，その対応について概説する．

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1 アルツハイマー病のBPSDの特徴

ADでは病初期から多彩なBPSDが生じることが知られており，なかでもアパシー，興奮，易刺激性，異常行動，妄想，抑うつなどの頻度が高い[1,13,18,23,33]．

ADのBPSDは認知症重症度によって異なることも示されており，アパシーや興奮，異常行動は認知症が重度になるほど頻度は高くなる[5,33,42]．妄想，幻覚も重度になるにつれて頻度が増すという報告が多い[5,29,42]．抑うつは中等度あるいは重度で頻度が高いとされている[5,33]．

ADのBPSDと発症年齢との関連については，65歳未満発症の若年性AD（early-onset AD；EOAD）において，高齢発症AD（late-onset AD；LOAD）と比較して妄想が有意に少ないとする報告[49]がある．最近筆者らは，EOAD患者におけるBPSDの特徴について報告した[48]．Neuropsychiatric Inventory（NPI）[6]を用いたEOAD患者における認知症重症度別のBPSD有症率と得点を表1と

表2に示す．LOADを対象とした先行研究[5,33,42]と比較して，EOADにおいては軽度の時期から抑うつが多くみられることが示された．このことからは，ADにおける抑うつには，就労や子育て，経済的問題など心理社会的な要因が大きく影響している可能性が考えられた．また，LOAD患者において重度でよりみられるとする報告が多い幻覚は，EOADでは中等度で最も出現するという結果であった．ADにおける幻覚は頭頂あるいは後頭皮質の機能低下と関連するとの報告[10,19]がある一方で，EOADは両側頭頂葉などの灰白質減少がLOADより重度であるとの報告[25]がある．このことを反映して，EOADにおいては認知症が重度となる以前から幻覚が悪化するパターンをとる可能性が考えられた．なお，興奮やアパシー，異常行動は，LOADにおける報告と同様，EOADにおいても認知症が重度となるにつれて悪化する傾向が確認された．これらはAD病理の進展をダイレクトに反映している可能性が示唆された．

表1　若年性アルツハイマー病患者における認知症重症度別のBPSDの有症率

	全体	軽度 (CDR 0.5〜1, n = 55)	中等度 (CDR 2, n = 17)	重度 (CDR 3, n = 20)
妄想	14.1%	12.7%	17.6%	15%
幻覚	8.7	1.8	23.5	15
興奮	26.1	20	23.5	45
抑うつ	39.1	41.8	47.1	25
不安	35.9	40	41.2	20
多幸	8.7	5.5	0	25
アパシー	82.6	76.4	82.4	100
脱抑制	5.4	1.8	0	20
易刺激性	33.7	32.7	29.4	40
異常行動	26.1	16.4	41.2	40

CDR：Clinical Dementia Rating

(Tanaka H, Hashimoto M, Fukuhara R, Ishikawa T, et al.: Relationship between dementia severity and behavioural and psychological symptoms in early-onset Alzheimer's disease. *PSYCHOGERIATRICS*, 2015 Mar 3. doi: 10.1111/psyg.12108. [Epub ahead of print] より改変引用)

② アルツハイマー病のBPSDへの対応の原則

ADに限ったことではないが，BPSDに対応する前に症状評価と標的症状の選択を行うことが肝要である[24]．NPI Caregiver Distress Scale（NPI-

表2　若年性アルツハイマー病患者における認知症重症度別のNPI下位項目得点

NPI項目	認知症重症度 軽度 (n = 55)	中等度 (n = 17)	重度 (n = 20)	p値	群間比較*
妄想	0.33 ± 1.04	1.59 ± 3.99	0.90 ± 2.79	0.127	
幻覚	0.02 ± 0.14	1.47 ± 3.39	0.90 ± 2.77	0.017	軽度＜中等度
興奮	0.67 ± 1.51	0.76 ± 1.68	3.60 ± 4.94	＜0.001	軽度，中等度＜重度
抑うつ	1.18 ± 1.88	1.47 ± 3.00	0.55 ± 1.10	0.34	
不安	1.40 ± 2.31	2.00 ± 3.39	0.95 ± 2.14	0.45	
多幸	0.13 ± 0.61	0	1.15 ± 2.83	0.013	軽度，中等度＜重度
アパシー	3.36 ± 3.19	6.29 ± 4.15	10.20 ± 2.75	＜0.001	軽度＜中等度＜重度
脱抑制	0.02 ± 0.14	0	1.45 ± 3.33	0.002	軽度，中等度＜重度
易刺激性	1.00 ± 1.81	0.65 ± 1.22	2.70 ± 4.05	0.014	軽度，中等度＜重度
異常行動	0.75 ± 2.08	2.88 ± 4.00	3.65 ± 4.89	0.001	軽度＜重度

数値はmean ± *SD*を示す．

NPI：Neuropsychiatric Inventory

*post hoc Tukey test

(Tanaka H, Hashimoto M, Fukuhara R, Ishikawa T, et al.: Relationship between dementia severity and behavioural and psychological symptoms in early-onset Alzheimer's disease. *PSYCHOGERIATRICS*, 2015 Mar 3. doi: 10.1111/psyg.12108. [Epub ahead of print] より改変引用)

D）日本語版[31]のような評価尺度でBPSDの内容と頻度，重症度そして介護負担を評価する．さらにその症状が急性に増悪しているのか，それとも慢性的にゆっくり悪化しているのかということを評価し，対応を急ぐべき症状かどうかを判断する．さらに，BPSDが疾患そのものによる症状なのか，環境要因などによって二次的に出現している症状なのか，あるいはその2つが相互に影響し合って出現しているものなのかを評価することによって，対応法を選択する．つまり，主たる原因が環境要因である場合には薬物療法は控え，環境調整のみで治療を試みる．一方，疾患そのものによる症状の場合には，どんなにケアの工夫をしてもそれのみでは改善できないことがよくあるので，慎重に見極める必要がある．次に，多くの場合，同時に出現している複数のBPSDのなかから治療をすべき標的症状を厳密に定めて，できるかぎり理論的な仮説から治療法を選択していく．標的症状となるのは，日常生活上で患者自身のリスクになるもの，介護負担が大きいもの，患者と介護者のQOLを下げるもの，高頻度に出現しているもの，などである．

1．非薬物療法

ADにおけるBPSDの多くは，認知症をもつ個人が周囲とのかかわりのなかで現れる症状であることを考慮すれば，BPSD治療はケアの工夫やリハビリテーション，環境調整などの非薬物療法が優先される[40]．非薬物療法のエビデンスは蓄積されつつあり，例として音楽療法は興奮の改善に有用であることが示されている．また，運動と心地よい体験は抑うつを減じ，身体活動への取組みは興奮を抑制できることが示されている．しかしながら，これらの報告は期間の短さや対象の少なさの点でいまだ十分とはいえない[28]．介護者への教育がADのBPSDを改善することは無作為化試験で示されている[14]．

2．薬物療法

2005年4月付けのアメリカ食品医薬品局（FDA）による死亡率上昇の勧告，そして2011年9月28日付けの厚生労働省の通達による「器質的疾患に伴うせん妄・精神運動興奮状態・易怒性」に対するクエチアピン，ハロペリドール，ペロスピロン，リスペリドンの保険適応外使用の容認など，BPSDに対する抗精神病薬の使用における混乱はいまだ続いている．現時点では，保険適応のない治療法であることを，本人ないし家族に十分説明して承諾を得たうえで，必要最少限の量を，できるかぎり短期間使用することに尽きると思われる[40]．

③ アルツハイマー病の代表的なBPSD
—— 発現機序とその対応 ——

1．アパシー

アパシー（無為，無関心，意欲の低下）はADの初期から最もよくみられる症状のひとつであり[23,33]，「趣味をしなくなった」「他人への関心が乏しくなった」などの変化で現れる．妄想や興奮などのいわゆる陽性症状と比較すると目立ちにくい症候であるが，放置すると引きこもり状態を形成しやすく，結果として生活リズムを崩したり，心身の廃用性変化を生じたりするきっかけとなるため，早期に患者の変化に気づき，対応することが重要となる．ADにおけるアパシーは前頭葉眼窩面・内側面，前部帯状回などの血流・代謝の低下や灰白質体積減少，アミロイドβ（Aβ）沈着との関連が報告されている[3,4,30,37]．アパシーへの対応としては，ドネペジルなどのコリンエステラーゼ阻害薬の有効性が数多く報告されており，通所介護などのケアとの併用によって相乗効果が期待される．

2．妄想

妄想もADでよくみられるBPSDであり，半数以上の患者に認められ[18]，内容としては物盗られ妄想などの被害妄想が多い．物盗られ妄想については，女性患者に多く，ほとんどの例で財布や通帳，印鑑など金銭にかかわる物を盗られたと訴え，身近な介護者が妄想の対象となりやすい[22]．ADにおける妄想についての画像研究はいくつかあり，

右半球や前頭葉の機能低下との関連を示すものが多いものの[27,36,39,46]，研究の間で一致していない．脳の器質的変化のみならず，病前性格や現在の生活環境などの心理社会的背景など，多方面からの検討が必要と思われる．ADの妄想と幻覚を含めたいわゆる精神病症状に対しては，リスペリドンやオランザピン，アリピプラゾールなどの非定型抗精神病薬の少量投与の有効性が報告されている[8,26,47]．しかしながらリスペリドン，オランザピン，クエチアピンを用いた多施設二重盲検ランダム化試験において，精神病症状や興奮への効果は限定的で，副作用と相殺される程度と結論づける報告[45]もある．副作用に留意し続け，投薬内容の見直しや減量の可能性を常に頭の片隅におきながら，慎重に治療を進める必要がある．

3．興奮

ADにおける興奮は，暴言，暴力，介護への抵抗といったかたちでも現れ，それらを含めてagitationと称されることもある．男性患者に多くみられ[11,12]，介護者の困窮に直結するため早期の対応が望まれる．画像研究においては報告により差はあるものの，前頭皮質や前・後部帯状回，島皮質，扁桃体そして海馬などの体積減少，血流低下との関連を示す報告が多い[4,21,50,51]．興奮にも非定型抗精神病薬の有効性は実証されており，興奮が強くただちに治療が必要な場合は，前述のかたちで非定型抗精神病薬を使用する．症状が比較的軽症の場合は抑肝散での治療が安全性の面で優れており推奨されるが[35]，甘草による偽アルドステロン症（低カリウム血症，浮腫）には注意が必要である．AD治療薬であるメマンチンが興奮などの抑制に有効とされており[17,52]，認知症重症度が中等度～重度のAD患者にはメマンチンを第1選択としてもよいと考えられる．最近，わが国では鎮咳薬として認可されているデキストロメトルファンとキニジンとの合剤を用いたプラセボ対照無作為化試験において，高い忍容性のもとADにおける興奮を有意に改善させたとの報告[7]が出されたが，NMDA受容体拮抗作用を有する点がメマンチンと共通している．

4．抑うつ

抑うつはADにおいてしばしばみられる症候であり[23,33]，うつ病の既往あるいは家族歴がある場合には，AD発病後に抑うつを伴うリスクが高くなるという報告[15]がある．ADにおける抑うつに関する画像研究は少なく，嗅内皮質と前部帯状回あるいは左中前頭皮質の体積減少との関連を示す報告[21,53]があるのみで，十分に解明はされていない．ADにおける抑うつは，特定の部位の機能低下というより心理社会的な要因が強いのかもしれない．ADの抑うつに対して種々の選択的セロトニン再取り込み阻害薬（SSRI）やセロトニン-ノルアドレナリン再取り込み阻害薬（SNRI），ノルアドレナリン作動性・特異的セロトニン作動性抗うつ薬（NaSSA）などの抗うつ薬が処方されるが，メタアナリシスによってセルトラリンとミルタザピンのプラセボと比較した優位性は否定されており[2]，今後さらなる検討が必要である．神経基盤もはっきりと解明されていないところを併せ考えると，心理社会的な要因の強さがうかがえる．本人が能力低下を過度に自覚しないような対応が重要である．

5．異常行動

徘徊に代表される異常行動もADで比較的よくみられる症候で，「落ち着きなくうろうろする」「タンスの中を探り衣類を出し入れする」など実用性の伴わないものであることが多い．前頭葉機能低下との関連を示す報告[38]のほか，画像研究においては眼窩前頭皮質の血流増加との関連が報告されている[44]．徘徊に対して非定型抗精神病薬が使用される場合があるが，有効性についてのエビデンスは乏しい．徘徊は原則ケアで対応すべき症候であり，行動の要因を多面的に検討して解決法を探ることが重要である．

6．睡眠障害

睡眠障害は1/4～約半数のAD患者にみられ[5,29]，総睡眠時間の減少，中途覚醒回数・時間の増加として観察される．そのメカニズムとしてはアセチ

ルコリン系をはじめとする種々の神経伝達系の障害に加え，メラトニン分泌リズムの機能異常による概日リズム異常[20,34]などが関連するとされている．ADの睡眠障害に対してベンゾジアゼピン系薬物が処方されることも多いが，その治療効果を支持するエビデンスは乏しい．とくに長時間型では日中の傾眠や筋弛緩作用による転倒などの危険性が高く，推奨されない．トラゾドンの少量投与やメラトニン作動薬であるラメルテオンがADにおける睡眠障害に有効との報告もあるが，エビデンスとしては弱く[32]，さらなる検討が望まれる．

おわりに

ADは他の認知症疾患と比較すると，進行が緩徐で，かつ認知症が最重度となるまで局所神経症候や錐体外路症状を認めにくく運動機能が保たれる特徴がある．そのため，その長い期間をいかに「穏やか」に生活していくかは，患者本人のみならず本人を取り巻く家族，介護者にとってもきわめて重要なことである．BPSDへの対応は認知症治療に携わる医師にとって最も大切な役割のひとつであり，薬物療法と非薬物療法および介護・ケアを駆使しながら日々最善の方法を模索し続ける必要がある．

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Original Research

Outcomes of Inpatient Treatment for Behavioral and Psychological Symptoms of Dementia in Alzheimer's Disease Versus Dementia With Lewy Bodies

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ABSTRACT

Objective: Most community-based studies have shown a more malignant clinical course for patients with dementia with Lewy bodies (DLB) than Alzheimer's disease (AD). We examined differences in outcomes between patients with DLB and AD hospitalized for the treatment of behavioral and psychological symptoms of dementia.

Method: A chart review was conducted of patients with either AD or DLB hospitalized in the acute psychogeriatric ward between January 2008 and December 2011 in Kahoku-City, Ishikawa, Japan. Outcome measures were discharge destinations and time to death. A diagnosis of AD was made according to *DSM-5* criteria, whereas a diagnosis of DLB was made according to the Consortium on DLB International Workshop criteria for probable DLB. Pharmacologic treatment was optimized under constant monitoring of patients. Cholinesterase inhibitors and yi-gan san were tried prior to antipsychotics in DLB patients.

Results: The study cohort consisted of 224 patients with AD and 106 with DLB. After matching for sociodemographic factors and cognitive and physical function, it was found that antipsychotics were less frequently used during hospitalization in patients with DLB than AD (63% vs 82%, respectively, $P < .01$), whereas cholinesterase inhibitors (88% vs 43%, $P < .001$) and yi-gan san (35% vs 20%, $P < .05$) were more frequently used in patients with DLB. There were no significant differences in discharge destinations between the 2 groups. The 5-year cumulative survival rates were similar in the AD and DLB groups (46.4% vs 45.7%, respectively, $P = .6225$).

Conclusions: Optimization of pharmacologic treatment during hospitalization could reduce the use of antipsychotics and improve the subsequent clinical course in DLB.

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Alzheimer's disease (AD) and dementia with Lewy bodies (DLB) are 2 of the most common types of dementia.[1–3] Previous studies have compared disease progression and treatment outcomes between AD and DLB[4–13]; most studies[4–10,13] have reported unfavorable clinical outcomes among patients with DLB, including a greater risk of admission to the medical hospital and shorter survival. One possible explanation for these observations could be vulnerability to neuroleptic sensitivity reactions,[14] which are characterized by a sudden onset of sedation and increased confusion and immobility, often leading to fatal consequences.[15]

It has been demonstrated that some psychiatric symptoms in DLB may respond to cholinesterase inhibitors.[16–18] Yi-gan san, a traditional Asian herbal medicine, has also emerged as a safer alternative to antipsychotics for the treatment of psychiatric symptoms and sleep disturbances in DLB.[19–21] Nevertheless, a study showed that antipsychotics are still prescribed more frequently to DLB patients despite the risk of neuroleptic sensitivity reactions.[22]

Most of the studies comparing the clinical course of DLB and AD have been conducted in community-based or outpatient settings, and these sorts of comparisons in hospitalized patients are rare. In Japan, the number of patients admitted to psychiatric hospitals because of behavioral and psychological symptoms of dementia has increased.[23] One advantage of inpatient treatment is that pharmacologic treatment can be optimized based on detailed observations of changes in symptoms, as well as signs of adverse reactions, while patients are being closely monitored under specialist care. In the present study, we retrospectively examined differences in outcomes between patients with DLB and AD who had been hospitalized for treatment of behavioral and psychological symptoms of dementia. We hypothesized that inpatient treatment could have a positive impact on the subsequent clinical course of patients with DLB.

METHOD

The medical records of patients who had been hospitalized in the acute psychogeriatric ward of Ishikawa Prefectural Takamatsu Hospital, Kahoku-City, Ishikawa, Japan, were reviewed. The institutional review board approved this retrospective analysis and waived the requirement for written informed consent.

Patients

Consecutive patients with AD and DLB who had been admitted to the acute psychogeriatric ward for treatment of behavioral and psychological symptoms of dementia between January 2008 and December 2011 were enrolled in the study. All patients had severe behavioral and psychological symptoms of dementia such that they could not be cared for in their own home or care facility, nor could they be treated in an outpatient setting. Patients with significant comorbid physical disease were judged to be

Clinical Points

- Clinical outcomes in patients with dementia with Lewy bodies after inpatient treatment for behavioral and psychological symptoms of dementia were comparable to those of patients with Alzheimer's disease.
- In optimizing pharmacotherapy, preferential use of cholinesterase inhibitors and yi-gan san in patients with dementia with Lewy bodies, and constant monitoring of neuroleptic sensitivity reactions under specialist care, could reduce the use of antipsychotics.

ineligible for hospitalization to the acute psychogeriatric ward in order to prioritize medical treatment for their physical problems. Patients who had primary neurologic or psychiatric disease other than AD and DLB, and those who had behavioral symptoms prior to cognitive decline, were excluded from the study. Patients with a history of hospitalization in the acute psychogeriatric ward of Ishikawa Prefectural Takamatsu Hospital were also excluded from the study.

Measures

In all patients, the following items were evaluated and recorded within 1 week of admission according to institutional protocol.

Demographics

Data regarding the patient's gender, age, living situation (including residency and family style before hospitalization), and relationship with his/her caregiver were obtained from an interview or a questionnaire administered by a psychiatric social worker to the family members or staff of the care facility or hospital. Residency before hospitalization was classified as the patient's own home, group home, care facility, or medical hospital. A group home is a care facility wherein a group of people live their daily lives essentially independently, with staff support only when needed. Family style refers to the people with whom the patient had lived. In the case of patients who had lived with family members other than their partner or with staff of a care facility, group home, or medical hospital, family style was classified as "other." The relationship with the caregiver was classified as partner, other family member, or staff.

Type of Dementia

A diagnosis of dementia was made by either of 2 experienced geriatric psychiatrists (T.K. and M.K.) based on an interview with the patients and family members or staff, physical and neurologic findings, laboratory data, and brain imaging. A diagnosis of AD was made according to the *DSM-5*, whereas diagnoses of DLB were made according to the Consortium on DLB International Workshop criteria for probable DLB.[1,24]

Primary Reason for Hospitalization

The behavioral problems causing distress to the caregiver and that were the primary reasons for hospitalization were recorded following interviews with the caregiver. Primary reasons for hospitalization were classified as combative behavior, overactivity, or apathy/depression. Combative behavior comprised physically or verbally aggressive behavior during or between care provision, such as hitting, kicking, biting, throwing things, cursing, and screaming. Overactivity included nonaggressive behavior that required monitoring, such as aimless wandering, trying to reach a different place, restlessness, or repetitive actions and mannerisms. Apathy/depression included serious apathetic or depressive behavior, such as severe loss of appetite, refusal to eat, refusal to take medication, or suicidal tendencies.[25]

Behavioral and Psychiatric Symptoms

Behavioral and psychiatric symptoms were evaluated by 2 geriatric psychiatrists (T.K. and M.K.) using the Behavioral Pathology in Alzheimer's Disease (BEHAVE-AD) rating scale.[26] The presence or absence of symptoms in each of 7 clusters comprising a subscale of BEHAVE-AD were recorded, including paranoid and delusional ideation, hallucinations, aggressiveness, activity disturbances, diurnal rhythm disturbances, affective disturbances, and anxieties or phobias.

Cognitive Function

Cognitive function was assessed by the geriatric psychiatrists in the acute psychogeriatric ward using the Mini-Mental State Examination (MMSE).[27]

Functional State of Daily Living

Activities of daily living (ADL) were scored by well-trained nursing staff according to the Nishimura Activities of Daily Living (N-ADL) scale,[28] which is one of the most used scales for the evaluation of ADL in Japan. In the N-ADL, 5 items are evaluated: walking/sitting, range of activities, dressing/bathing, eating, and excretion. Each item is scored from 0 to 10 points, with the total (maximum score 50) taken as the N-ADL score. A higher score indicates better functioning in ADL. Nursing staff rated the reliability of the scale when completed as good.[28]

Intervention and Monitoring

Nonpharmacologic approaches. Nonpharmacologic approaches were implemented for all patients following admission. In addition to the aforementioned evaluation, medical, psychological, and environmental assessments were conducted to identify modifiable factors that could potentially exacerbate behavioral and psychological symptoms of dementia. We evaluated the presence of pain, inadequate nutrition, infection, and other medical problems. The medication profile for each patient was also reviewed. Interviews were conducted with each patient and key informants to elucidate changes in daily activities and roles at home, previous interests, personality traits, inappropriate coping and communication by caregivers (eg, yelling, harsh tone, criticizing), and the use of care resources. Based on the outcomes of these assessments, we tried to eliminate

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any conditions identified as contributing to behavioral and psychological symptoms of dementia. Occupational therapy was provided to patients to help them engage in meaningful or pleasurable activities, tapping into preserved capabilities or previous interests. We also provided education to the caregivers to improve their understanding of the disease and their communication with the patient.

Pharmacologic interventions. The principles of our pharmacologic approach were as follows. After comprehensive assessment and symptom observation in the first week, patients received pharmacologic intervention based on clinical indications. For DLB patients, cholinesterase inhibitors were tried first. If the cholinesterase inhibitor was not sufficiently effective, yi-gan san was added. Quetiapine was initiated at a low dose (eg, 12.5 or 25 mg/d) and slowly titrated if the combination of the cholinesterase inhibitor and yi-gan san was ineffective or if more acute symptom control of behavior was required. When sensitivity reactions were observed, quetiapine was tapered to a lower dose or discontinued. Switching to other antipsychotics was minimized. For patients with AD, the use of cholinesterase inhibitors and yi-gan san was left to the discretion of individual psychiatrists. The use of quetiapine in patients with AD followed the strategy used in the case of DLB. The use of antidepressants, mood stabilizers, and hypnotics was allowed in both AD and DLB patients.

Monitoring. The nursing staff provided 24-hour care and monitored the patients' condition under a 3-shift system. Careful attention was paid particularly to the patients' ability to walk and eat, as well as their ability to concentrate on daily living activities and to detect signs of neuroleptic sensitivity reactions, including extrapyramidal symptoms and cognitive fluctuation. A psychiatrist was present throughout the day shift at the acute psychogeriatric ward, and each patient was examined by a psychiatrist multiple times a day in a regular and timely manner. Daily meetings were held to share information between professionals.

Mortality Surveillance

As part of routine practice, we inspect daily the death notices in the local newspaper *Hokkoku Shimbun* to monitor the incidence of death among patients treated at the Ishikawa Prefectural Takamatsu Hospital. The death notices in *Hokkoku Shimbun* provide a person's name and address, date of death, and information on funeral or memorial services. A death notice is submitted by the municipal office to *Hokkoku Shimbun* every time a municipal resident dies. The newspaper offers to publish death notices for free to the bereaved family. We have confirmed with the *Hokkoku Shimbun* office that only rarely do families refuse the offer of publication of a death notice.

Statistical Analysis

The main clinical endpoints in the present study were (1) discharge destinations and (2) time to death. Other endpoints included psychotropic medications prescribed during hospitalization and time to discharge.

Data management and statistical calculations were performed using Stata version 11.0 (Statacorp, College Station, Texas). In the case of descriptive statistics, differences between AD and DLB were tested using a t test for age, MMSE score, N-ADL score, and dose of antipsychotics. The χ^2 test was used to analyze frequency data.

To enable proper comparisons, the 2 groups (AD vs DLB) were matched for demographic and environmental factors, as well as cognitive and physical state. We used propensity score matching methods[29] to produce matched pairs for the AD and DLB groups. To estimate the propensity scores, age, sex, residency before hospitalization, family style, caregiver's relationship to the patient, MMSE score, and N-ADL score were used as covariates of exposure (DLB) in a logistic regression model. Propensity score estimation and matching were performed using the Stata PSMATCH2 program. Patients with DLB were matched with AD patients on the basis of estimated propensity scores using the nearest neighbor approach within a caliper of 0.02. After matching on propensity scores, the Wilcoxon signed rank test was used to test the significance of differences in age, MMSE score, N-ADL score, and dose of antipsychotics, whereas the McNemar test or multinomial logistic regression analysis was used to analyze differences in frequencies.

Estimates of hospital stay probability were calculated according to Kaplan-Meier methods with the time from admission to discharge. Death during hospitalization or transfer to a medical hospital due to deterioration of a patient's physical condition was treated as a censor. A log rank test was used to evaluate the differences in time to discharge. In survival analysis, Kaplan-Meier estimation was used with time from admission to death, and the log rank test was used to test the significance of differences. No observed death until the study end was treated as a censor. We also performed multivariate analysis to determine covariates with an effect on time to death. In addition to the type of dementia (AD or DLB), the variables used to construct propensity scores were included in the multivariate Cox proportional hazards model. In this model, backward elimination was used to establish a cutoff P value of .10.

Statistical significance was defined as 2-tailed $P < .05$. Bonferroni correction was used to adjust P values for multiple comparisons.

RESULTS

Before Matching

In all, 330 patients were identified as eligible for the study: 224 with AD and 106 with DLB. The demographic characteristics and clinical manifestations before matching are listed in Table 1. The 2 groups were similar in age, gender, residency before hospitalization, family style, and caregiver relationship. Regarding cognitive and physical function, although DLB patients had a higher MMSE score, they did not differ from AD patients in terms of the N-ADL score. Combative behavior was more frequently the primary reason for hospitalization of AD patients, whereas overactivity was

Table 1. Demographic Characteristics and Clinical Manifestations of Patients With Alzheimer's Disease (AD) and Dementia With Lewy Bodies (DLB) Hospitalized for Treatment of Behavioral and Psychological Symptoms of Dementia Before and After Matching

	Before Matching[a]		After Matching[b]	
Variable	AD (n = 224)	DLB (n = 106)	AD (n = 102)	DLB (n = 102)
Age, mean ± SD, y	82.7 ± 6.5	83.0 ± 5.9	84.7 ± 5.7	83 ± 6.0
Men, n (%)	71 (32)	34 (32)	32 (31)	32 (31)
Residency before hospitalization, n (%)				
Own home	148 (66)	69 (65)	67 (66)	66 (65)
Group home	14 (6)	8 (8)	12 (11)	7 (7)
Care facility	41 (18)	19 (18)	16 (16)	19 (19)
Medical hospital	21 (9)	10 (9)	7 (7)	10 (10)
Family style, n (%)				
Alone	13 (15)	12 (12)	14 (14)	13 (13)
With partner only	12 (12)	16 (15)	14 (14)	14 (14)
Other	76 (73)	76 (73)	74 (73)	75 (74)
Caregiver's relationship to patient, n (%)				
Partner	33 (14)	23 (22)	14 (14)	21 (21)
Other family member	121 (54)	45 (42)	51 (50)	44 (43)
Staff	70 (31)	38 (36)	37 (36)	37 (36)
MMSE score, mean ± SD	10.8 ± 7.0	13.5 ± 7.5*	12.9 ± 6.9	13.0 ± 7.3
N-ADL score, mean ± SD	27.5 ± 11.6	26.2 ± 10.1	25.6 ± 10.9	26.2 ± 10.3
Primary reason for hospitalization, n (%)				
Combative behavior	121 (54)	33 (31)**	58 (57)	32 (31)***
Overactivity	73 (33)	50 (47)*	31 (30)	48 (47)
Apathy or depression	30 (13)	23 (22)	13 (13)	22 (22)
Behavioral and psychological symptoms, n (%)				
Delusions	62 (28)	29 (27)	25 (25)	28 (27)
Hallucinations	19 (8)	56 (53)**	7 (7)	55 (55)**
Aggressiveness	151 (67)	55 (52)***	69 (68)	53 (52)*
Activity disturbance	136 (60)	61 (58)	54 (53)	59 (58)
Diurnal rhythm disturbance	137 (61)	66 (62)	62 (61)	63 (62)
Affective disturbance	62 (28)	33 (31)	36 (35)	32 (31)
Anxiety and phobias	55 (25)	28 (26)	23 (23)	27 (26)

[a]Dichotomous characteristics were compared using the χ^2 test; continuous characteristics were compared using *t* tests.
[b]Dichotomous characteristics were compared using the McNemar test or multinomial logistic regression analysis; continuous characteristics were compared using the Wilcoxon signed rank test.
*$P < .05$.
**$P < .001$.
***$P < .01$.
Abbreviations: MMSE = Mini-Mental State Examination, N-ADL = Nishimura Activities of Daily Living.

Table 2. Psychotropic Medications Used in Patients With Alzheimer's Disease (AD) and Dementia With Lewy Bodies (DLB) Hospitalized for Treatment of Behavioral and Psychological Symptoms of Dementia Before and After Matching

	Before Matching[a]		After Matching[b]	
Variable	AD (n = 224)	DLB (n = 106)	AD (n = 102)	DLB (n = 102)
Prescribed antipsychotics, n (%)	169 (75)	66 (62)*	84 (82)	64 (63)**
Dose of antipsychotics, mean ± SD, mg/kg[c]	3.1 ± 2.8	3.2 ± 3.6	2.7 ± 2.4	3.2 ± 3.7
Prescribed cholinesterase inhibitors, n (%)	121 (54)	92 (87)***	44 (43)	90 (88)***
Prescribed yi-gan san, n (%)	24 (11)	38 (36)***	20 (20)	36 (35)*

[a]Dichotomous and continuous characteristics were compared using χ^2 and *t* tests, respectively.
[b]Dichotomous and continuous characteristics were compared using the McNemar test and Wilcoxon signed rank test, respectively.
[c]Daily dose of antipsychotics in chlorpromazine equivalents employed at the maximum in individuals using antipsychotics.
*$P < .05$.
**$P < .01$.
***$P < .001$.

more frequently the reason for DLB patients. Regarding behavioral and psychological symptoms of dementia, DLB patients were more likely to present with hallucinations, whereas AD patients were more likely to present with aggressiveness.

With regard to psychotropic medications prescribed during hospitalization (Table 2), the data before matching showed a less frequent use of antipsychotics, but a more frequent use of cholinesterase inhibitors and yi-gan san in DLB patients. There was no difference in the daily dose of antipsychotics. In AD patients, the types of antipsychotics most frequently used during hospitalization were quetiapine (in 139 patients, 82%), followed by risperidone (22, 13%), olanzapine (10, 6%), and haloperidol (8, 5%).

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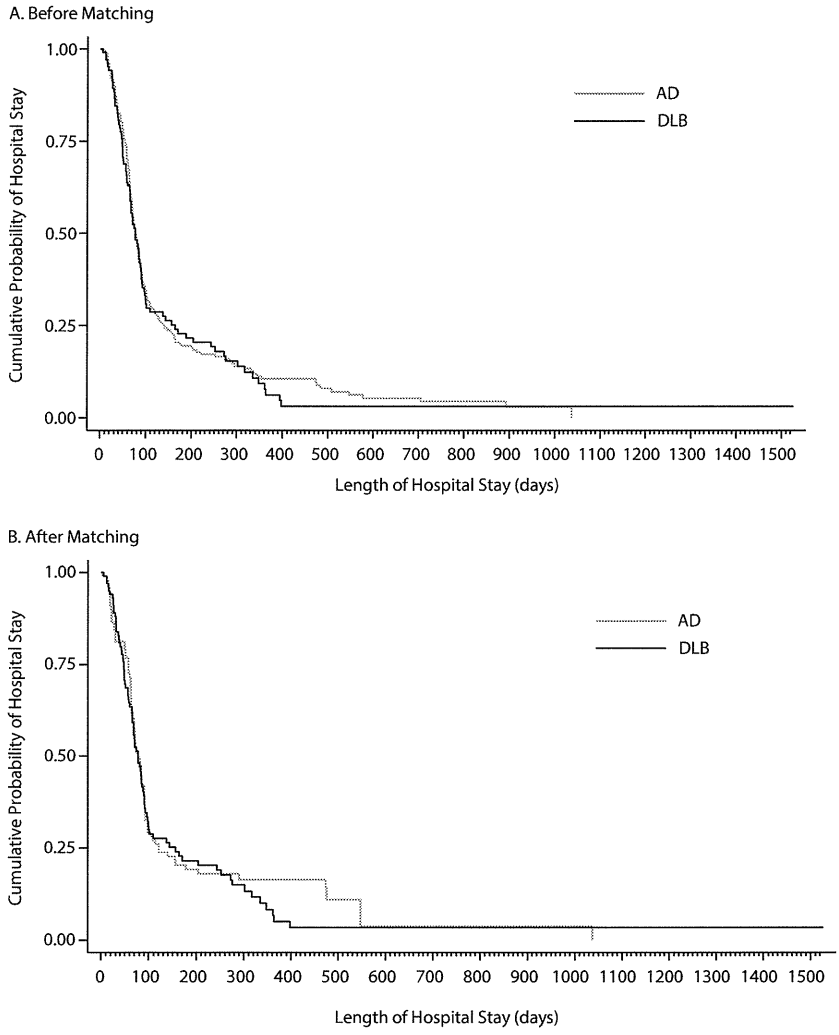
Table 3. Discharge Destination of Patients With Alzheimer's Disease (AD) and Dementia With Lewy Bodies (DLB) Hospitalized for Treatment of Behavioral and Psychological Symptoms of Dementia Before and After Matching[a]

	Before Matching[b]		After Matching[c]	
Discharge Destination	AD (n = 224)	DLB (n = 106)	AD (n = 102)	DLB (n = 102)
Own home	74 (33)	37 (35)	30 (29)	35 (34)
Group home	36 (16)	20 (19)	23 (23)	20 (20)
Care facility	76 (34)	32 (30)	32 (31)	30 (29)
Medical hospital	31 (14)	16 (15)	13 (13)	16 (16)
Death during hospitalization	7 (3)	1 (1)	4 (4)	1 (1)

[a]Data are presented as n (%).
[b]Dichotomous characteristics were compared using the χ^2 test.
[c]Dichotomous characteristics were compared using a multinomial logistic regression analysis.

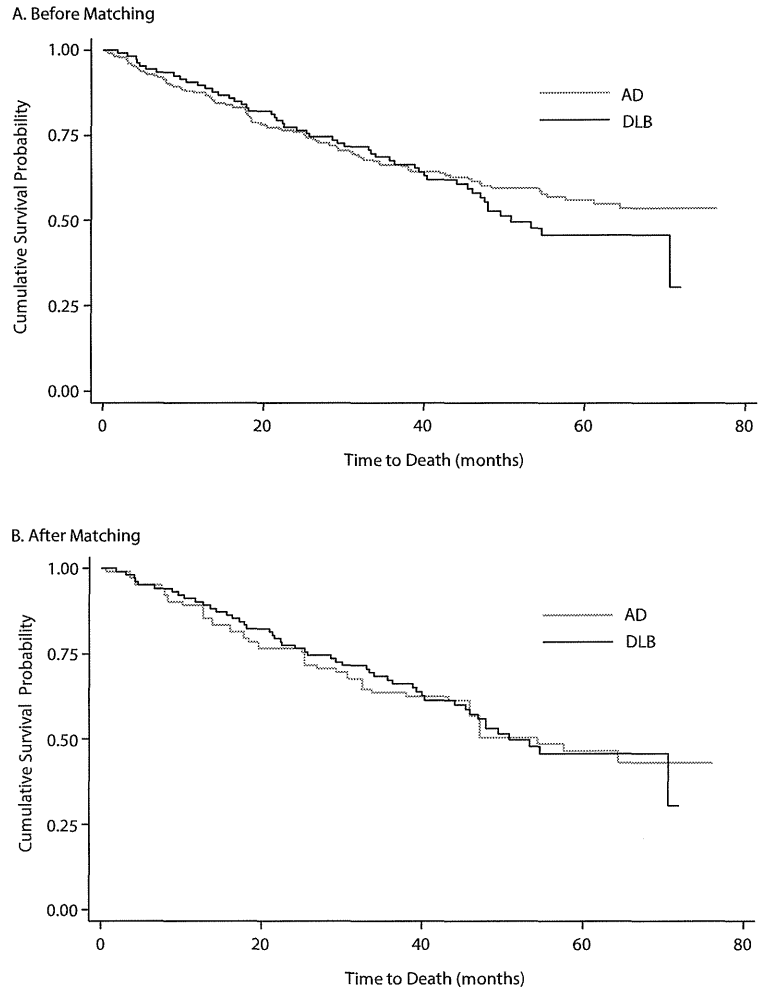
Figure 1. Cumulative Probability of Hospital Stay Between Patients With Alzheimer's Disease (AD) and Dementia With Lewy Bodies (DLB)



In DLB patients, quetiapine was the most frequently used antipsychotic (in 63 patients, 95%), followed by risperidone (2, 4%) and haloperidol (2, 4%) and olanzapine (1, 1%) and aripiprazole (1, 1%).

Table 3 lists the discharge destinations of the 2 groups. There were no significant differences in the incidence of discharge to a patient's own home, group home, care facility, or medical hospital or death during hospitalization between the 2 groups. Kaplan-Meier analysis (Figure 1A) revealed that the length of hospital stay (LOS) was equivalent between AD and DLB patients (median [95% CI] LOS: 77 days [70–84 days] vs 77 days [66–89 days], respectively, $P = .7579$). Kaplan-Meier analysis on cumulative survival probability is shown in Figure 2A. There was no significant

Figure 2. Cumulative Survival Probability Between Patients With Alzheimer's Disease (AD) and Dementia With Lewy Bodies (DLB)



difference in time to death between AD and DLB patients (5-year cumulative survival probability [95% CI] from admission: 56.1% [48.7%–62.8%] vs 45.7% [34.5%–56.2%], respectively, $P = .3261$).

After Matching

Matching on propensity score resulted in 102 matched pairs. Demographic characteristics and clinical manifestations after matching are listed in Table 1 and indicate that the 2 groups were balanced in terms of age, gender, residency before hospitalization, family style, caregiver's relationship to the patient, N-ADL score, and MMSE score. Even after matching, combative behavior was more frequently the reason for hospitalization of AD patients, whereas the difference in the prevalence of overactivity disappeared between the 2 groups. Among behavioral and psychological symptoms of dementia, the predominance of hallucinations in DLB patients and aggressiveness in AD patients persisted. As seen before matching, antipsychotics were less frequently used in DLB patients, whereas cholinesterase inhibitors and yi-gan san were more frequently used (Table 2).

The incidence of discharge to each destination was similar between the 2 groups (Table 3). The LOS was equivalent between AD and DLB patients (median [95% CI] LOS: 77 days [65–90 days] vs 77 days [66–89 days], respectively, $P = .9136$, Figure 1B). There was no significant difference in time to death between AD and DLB patients (5-year cumulative survival probability [95% CI]: 46.4% [34.9%–57.2%] vs 45.7% [34.2%–56.5%], respectively, $P = .6225$, Figure 2B).

Effects of DLB on Time to Death

Multivariate analysis using Cox proportional hazards model identified age, male gender, and N-ADL score as variables independently associated with time to death (for age, hazard ratio [HR] [95% CI] = 1.08 per year increase [1.05–1.11], $P = .000$; for male gender, HR = 2.97

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[2.10–4.19], $P = .000$; for N-ADL score, HR = 0.98 per unit increase [0.97–1.00], $P = .014$). DLB was not independently associated with time to death.

DISCUSSION

The results of the present study demonstrate that the outcomes of DLB patients after admission for the treatment of behavioral and psychological symptoms of dementia do not differ from those of AD patients. This finding is inconsistent with the results reported by most community-based studies,[1,5–10,13] which found a more malignant clinical course for DLB patients.

In contrast with the results of the population-based studies, we were able to prescribe antipsychotics less frequently to DLB patients, which potentially lowered the risk of neuroleptic sensitivity reactions. As part of our treatment policy to reduce the use of antipsychotics, cholinesterase inhibitors and yi-gan san were used preferentially in DLB patients. Furthermore, the inpatient setting allowed constant monitoring of patients under specialist care, so that signs of neuroleptic sensitivity reactions could be detected and antipsychotics tapered or discontinued accordingly. In the community, levels of knowledge and clinical experience with DLB vary considerably among care practitioners. Signs of neuroleptic sensitivity reactions are often unrecognized or even interpreted wrongly as a deterioration of primary symptoms. These signs may not be observed even by experienced clinicians during brief consultations with patients.[30]

Regarding behavioral and psychological symptoms of dementia, the present study showed a higher prevalence of aggressiveness in AD than DLB patients, which could be associated with more frequent use of antipsychotics in AD. This finding is attributed to the fact that most AD patients who do not exhibit aggressiveness can be managed within community care systems, which, in Japan, were originally established with the intent of caring for those with AD.

In the present study, survival time was estimated from the time of hospital admission, whereas the majority of previous studies estimated survival from disease onset or from the time of diagnosis. The apparent discrepancy between the present and previous studies may be due to methodological differences. However, the validity of estimating survival from disease onset or diagnosis has been questioned because demented patients and their caregivers often have difficulties pinpointing precisely when the symptoms appeared[13,31]; difficulties typically emerge gradually and can be subtle for months or even years before the initial hospital visit.[13] Stubendorff et al[13] proposed the validity of using a certain cognitive level as the benchmark in a survival study. In view of these considerations, we matched AD and DLB patients in terms of their MMSE scores in addition to environmental factors or physical state.

The present study has several limitations that should be acknowledged. Because of the retrospective nature of the study, the information available was limited. In particular, we did not use detailed measures, such as the Dementia Cognitive Fluctuation Scale[32] or the Unified Parkinson's Disease Rating Scale,[33] to evaluate the incidence and severity of neuroleptic sensitivity reactions. Although it is generally known that most common causes of death in DLB patients include aspiration pneumonia and fall-related injury,[10] which are closely associated with neuroleptic sensitivity reactions, the cause of death for the patients in the present study was not available. Furthermore, we implemented nonpharmacologic approaches in both AD and DLB patients, and this potentially ameliorated some of the symptoms. However, the effect was not systematically evaluated. Finally, this study was conducted in a particular region in Japan. Thus, the generalizability of the results could be questioned. A future well-designed, multicenter study could be warranted to confirm the findings reported herein.

In conclusion, the outcomes for DLB patients after admission for the treatment of behavioral and psychological symptoms of dementia are comparable to those of AD patients. This finding could be attributed to optimization of pharmacologic treatment under close monitoring by specialists during the period of hospitalization. The findings of the present study also highlight the importance of providing care practitioners in the community with a correct understanding of DLB and its neuroleptic sensitivity reactions.

Drug names: aripiprazole (Abilify), haloperidol (Haldol and others), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal and others).

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