タリングしていくことが求められる．現在，SHの定義は確立されていないが，治療介入の必要性からも，今後，SHの基準について検討していく必要がある．

PPHに関しては，DLBで食事による有意な血圧低下が認められた．PPHは，同じレビー小体病のスペクトラムであるパーキンソン病の運動症状の重症度が高い例に認められる[16]．食事中や食後にぼんやりとしたり，めまいがする，食事が進まなくなる，ぐったりする，などの症状が認められた場合には，PPHの可能性を考えるべきである．

以上述べたように，DLBでは，体位変換時および食事により血圧が変動することが明らかになった．これらの血圧変動は，日常生活にさまざまな問題を引き起こすだけでなく，予後にもかかわるため重要である．

2）排尿

DLBでは，女性で残尿感，排尿のしにくさが多く，その結果，排尿状態の満足度が低下していた．女性のみに有意な群間差があったのは，前立腺肥大や尿道の長さが影響する男性に比べて，自律神経障害による排尿障害をより純粋に反映しているためと考えられた．

日中，夜間の頻尿や切迫性尿失禁は，DLBでしばしば認められる[21,28]．切迫性尿失禁はDLBの53%で認められ，DATよりも高率に合併することが報告されている[20]．

排尿の問題は生活の質を大きく損なう問題であり，適切な薬物的，非薬物的治療が重要である．

3）排便

DLBでは，緩下薬を用いても調整がつきにくい頑固な便秘を有することが示唆された．

DLBでは，長期にわたり頑固な便秘に悩むことが多い．Incidental Lewy body disease（ILBD：生前パーキンソニズムを認めず，剖検で神経系にレビー小体が認められる病態で，発症前のレビー小体病と考えられる）においても腸管を含む末梢の自律神経系にα-シヌクレイン沈着がみられること[4,25]，レビー小体病では病早期より腸管蠕動運動障害を含む自律神経障害が認められること，高率に便秘を認めることが報告されている[1]．

便秘は，時に腸閉塞や，腸管穿孔など命にかかわる問題を引き起こす場合もある．便秘の有無やその程度について積極的な聴取と介入を行うことが重要である．

4）体温調整，発汗

本研究では，DLBで体温の調整がしにくくなっていることが示された．

DLBの発汗障害は四肢に多いとされ[26]，四肢遠位部での発汗調整を担う自律神経機能が低下しているとする報告[2]と矛盾しない．発汗過多については，顔，首，体幹で多くみられるが[12]，発汗低下部位，過多部位については一定の見解がない．

体温調整や発汗の異常は，高齢の人に多い脱水を重症化させる可能性がある．医療的な検索を行ったうえで，生活上の工夫について適切な助言を行うべきである．

2．睡眠

DLBでは，朝の目覚めがしばしば悪い．これは，DLBで伴いやすい抑うつ，悪夢，RBDや，睡眠時無呼吸症候群と関連することも推察された．本研究においてもその頻度の高さが改めて確認され，また睡眠薬や抗不安薬が修飾していることが示唆された．特発性RBDを長期追跡することで神経変性疾患を早期に発見できる可能性も報告されており[19]，今後注目していくべきである．

せん妄については，DLB群で，よりせん妄に近い状態であることが示された．熟眠感と互いに関連している可能性やRBDとの関連も疑われる．

まとめ

以上，本研究では，DLBの自律神経および睡眠に関する状態像を網羅的に検討した．その結果，血圧，排尿，排便，発汗における自律神経障害および睡眠障害は，DAT，NDに比して，DLBにおいて顕著に認められた．本研究の評価項目は血圧測定と聞き取り項目であり，得られた知見は日常臨床で活用しやすいと考える．

本研究の対象となった各群の年齢，性別には有意差を認めず，また，ADL，認知機能の低下は，

DLB群とDAT群の間で同等であった．抑うつについて，DLB群で，ND群やDAT群と比較して有意に得点が高かったのは，疾患の性質そのものを反映していると考えられた．これらより，サンプリングの等質性に問題はないと考えられた．

DLBの人が抱える身体症状はしばしば気づかれにくいが，日々の暮らしにくさに直結する問題であり，日常診療における自律神経障害の評価と医療介入は重要である．

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Autonomic dysfunction and sleep in dementia with Lewy bodies (DLB)

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Objective : To assess autonomic function and sleep in persons with DLB

Methods : We studied 27 pairs each consisting of a person with DLB and his/her carer, 15 pairs each consisting of a person with dementia of Alzheimer type (DAT) and his/her carer, and 17 non-demented (ND) control subjects at eight medical institutions. Autonomic functions (blood pressure, urination, bowel movement, and body temperature regulation/sweating) and sleep were evaluated.

Results : In the DLB group only, blood pressure elevation at the time of conversion from a sitting position to decubitus and blood pressure decrease at the time of the conversion from decubitus to a standing position showed a significant change. In women, the I-PSS total score and QOL score in the DLB group were significantly higher than those in the DAT group. In the case involving taking laxative agents regularly, the DLB group showed significantly less stool frequency than the ND group. There were significantly many complaints of heat retention in the DLB group. There were also many persons in the DLB group that felt bad when waking up in the morning.

Conclusion : Autonomic dysfunction and sleep disorder are frequently observed in the DLB group and should be evaluated for possible intervention.

Key words : dementia with Lewy bodies, autonomic dysfunction, sleep disorder

トピックス　レビー小体型認知症

問診に役立つレビー小体型認知症のスクリーニングとその意義

安田朝子
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はじめに

認知症の当事者が積極的に発信し、社会を動かし始めている。スコットランドを拠点とするScottish Dementia Working Group（ＳＤＷＧ）や、合衆国、カナダ、オーストラリアなど多国籍の人で構成されるDementia Alliance International（ＤＡＩ）など、認知症の当事者によるワーキンググループが、認知症の人のための制度改革やサービス改善、認知症（の人）に対する偏見の払拭、ＱＯＬ向上のための活動等を行っている。これらのグループはすべての認知症の人に開かれ、活動の広がりをみている。本年10月17日には、本邦初の認知症当事者団体である「日本認知症ワーキンググループ」が発足した。わが国にも、認知症の人の視点抜きには語れない時代が到来したと言える。

現在、わが国における認知症の人の数は４６２万と推定され、Mild Cognitive Impairmentを含めた数は８００万人以上とも言われる。[1] 今や、認知症の人みずからが医療にかかる時代となってきている。そこでは、他の疾患と同じように、認知症の人が自身の言葉で自身の問題を語る姿が当たり前のものとなる。しかし、現行の認知症にかかわるスクリーニング検査は、認知機能

検査のほかは他覚的評価が主である。

一方、英国（イングランド）の認知症国家戦略では、効果測定の最終的なアウトカム指標として「認知症の当事者の視点に立った9つの質問（『私は早期に認知症の診断を受けた』『私は尊厳と敬意を持って接せられている』他）」が位置付けられている。[2]

これからの認知症の人への支援は、認知症の人がどのような利益を得ることができたのか、その生活に根ざした効果測定が求められている。同様に、認知症の人がどのような体験をしているのかを反映した上で、医学的妥当性検討がなされたスクリーニング検査の必要性が高まっている。そこで本稿では、DLBに注目して作成されたSDI-DLB（the Subjective Difficulty Inventory in the daily living of people with DLB）[3]を紹介する。

SDI-DLBについて

1. SDI-DLBの開発

これまでの認知症医療では、アルツハイマー型認知症（dementia with Alzheimer's type：DAT）を念頭に、もの忘れやそれに伴うBPSDを主たる臨床像とした介入と支援が取り組まれてきた。しかし、認知機能の変動、幻覚および身体状態の変化など、DATとは異なる症状を特徴とするレビー小体型認知症（dementia with Lewy bodies：DLB）に対しては、スクリーニングおよび支援に関する測定の基盤は十分に整備されていない。また、DLBはその特徴的な症状のために、病初期より日常生活上の困難を感じやすいことも予想される。

以上をふまえ、SDI-DLBは、DLBの人の生活のしづらさを高い感度で評価し、生活面からスクリーニングすることのできるツールとして開発された。開発の経緯は次の通りである。

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(1) Consensus Method に沿い、まず、認知症の在宅医療を主とする医師、看護師、ケアマネジャー、臨床心理士および認知症当事者団体に所属する看護師の計6人のパネルメンバー（PM）から、各自が知る「認知症の人が体験した生活のしづらさ」に関するエピソード255件を収集。

(2) PMとは独立したファシリテーター（FT）によるカテゴリー分類と重複整理を通じ、92件の代表的エピソードを抽出。

(3) DLBの人によりよく当てはまる項目を選定するための3回のPM協議を通じ、SDI-DLB使用項目45項目を決定。

(4) 表①に示す医療機関の協力を得て、60歳以上のDLB群27人、DAT群15人、ND（認知症ではない人）群16人の3群を対象に45項目のSDI-DLBを実施。

(5) 合計得点のパーセンタイル順位による高群、中群、低群の通過率（0～4点）を確認した結

果と、臨床での利便性を考慮した項目数の点から、3群ともに通過率が低く（1・8点未満）、床効果が認められた25項目を除外した20項目をSDI-DLBの最終項目として採用（表②）。

2. SDI-DLBの信頼性および妥当性

SDI-DLBの信頼性を検証するため、再検査群23人における合計得点のICCを算出した。ICC＝0・89（95％信頼区間：0・72～0・96、p<0.01）であり、十分な相関が示された。また、α係数は0・94であり、内的整合性も十分に示された。

次に、認知症疾患との基準関連妥当性を検証するため、各群のSDI-DLB得点の平均値を多重比較した。その結果、DLB群はDAT群およびND群に比べて有意にSDI-DLB得点が高いことが示された。また、MMSE得点、Stroop課題正答率、PSMS得点、EQ-5D効用値、GDS得点、NPI合計得点と幻覚および認知機能の変動に関する下位尺度得点との間に、理論的に整合する方向でそれぞれ有意な相関（±0・32以上）が認められた。

3. SDI-DLBの有用性

DLB群27人とneurological control（DAT＋ND群）31人の2群における曲線下面積（area under the curve：AUC）は0・86（95％信頼区間：0・76～0・96、p<0.01）であり、SDI-DLBの十分な予測能が示された（図③）。また、cut off値を15／16点と設定した場合の感度は0・88、特異度は0・79であり、最も適切な値であった。DLB群のSDI-DLB得点は25パーセンタイルから最大値（68点）までcut off値以上に含まれ、合計得点範囲において広く分布した（図④）。

SDI-DLBの意義

SDI-DLBは、DLBの人が体験する生活のしづらさを十分に測定し、またDLBスクリーニングに有用であるだけでなく、一人ひと

② SDI-DLB

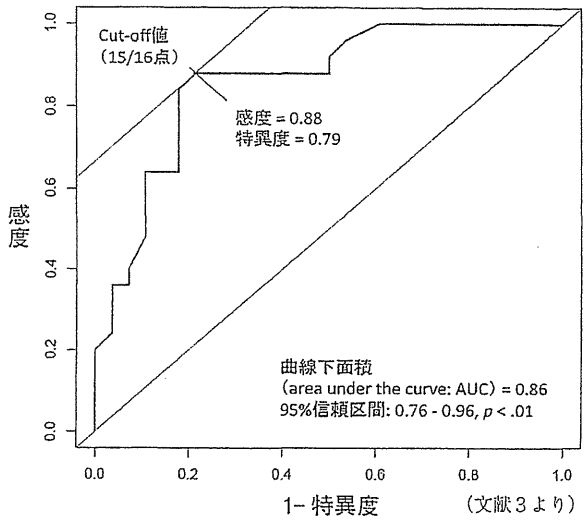
1	以前に比べて、普段の会話やテレビ・映画のセリフが早く感じ、ついていけない
2	階段や段差などで、足を上げる高さが合わずに足がもつれてしまう、あるいは踏み外してしまう
3	独り言をうわ言のように言ってしまう
4	今まで何気なくできていたことを失敗してしまう（ふと気づくと、物を入れ過ぎたり、取り間違えたりしてしまうなど）
5	一日中ぼんやりしている日がある
6	以前に比べて、一つの作業をやり遂げることがむずかしい
7	以前に比べて、ささいなことでひどくいらいらしてしまう
8	現実の出来事なのか、夢の中の出来事なのか、区別がつかない
9	一つのことに集中していると（本を読んだり、作業をしていると）、すぐに疲れてしまい続かない
10	急にぼんやりする、あるいはぼんやりしているとまわりの人に言われる
11	電話先が騒がしいと、以前に比べて、相手がなにを話しているのかわからない
12	一度に多くの情報があると、必要な情報を見つけることがむずかしい（看板が多いと必要な目印を探せない、たくさんのことが書かれたチラシのうちどこを見てよいかわからない、など）
13	以前に比べて、ささいなことでひどく落ち着かなくなる
14	歩いていると、どちらに進めばよいか迷ってしまったり、どの方向に進んでいるのかわからなくなってしまう
15	以前なら何でもなかったようなことが、集中しないとうまくいかない
16	以前に比べて、作業中に横から口を出されると、集中して取り組めない
17	以前に比べて、なじみのない人と会ったり話をしたりするとひどく疲れやすい
18	自分の体の向きや姿勢がわからず、着替えがむずかしかったり、ベッドやイス、便座に座れない
19	以前に比べて、なじみのない場所に行くとひどく疲れやすい
20	一度気になることがあると、以前と比べてそのことが頭から離れない

・各項目を5段階（まったくない0点、ほとんどない1点、ときどきある2点、ややある3点、いつもある4点）で評価する。合計得点は0～80点。高得点であるほど生活のしづらさを感じていることを示す。合計得点15点以下／16点以上をcut off値とし、16点以上であればDLBが疑われる。
・所要時間は約10分。SDI-DLBは本人による評価を主とする。しかし、介護者も同席して補完的に評価に加わることで、記憶障害等によって本人のエピソード想起が困難な場合や質問内容の理解が難しい場合には、具体的なエピソードに基づいて評価値の一致がみられるよう配慮する。

（文献3より）

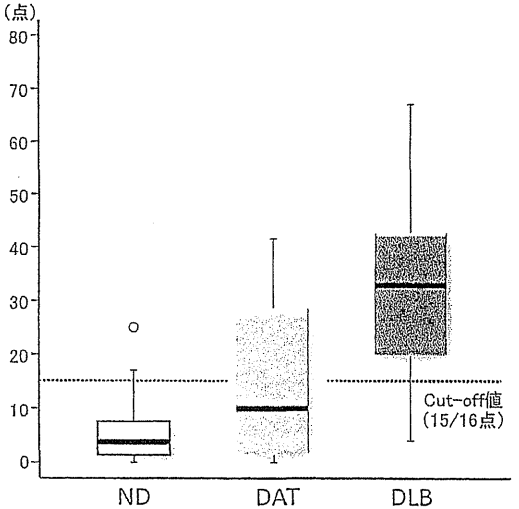
りの生活のしづらさを知る問診のツールともなる。症候上の特徴と関係する具体的な生活のしづらさを知ることにより、医療においてより重要な視点であるQOLの側面から認知症の人の理解を進めることができる。SDI-DLBを実施することが、認知症の人の悩みや困っていることに耳を傾けるきっかけとなりうる点も、これまでの測定法とは大きく異なる。具体的なエピソードを通じてこれを関係者と共有することで、認知症の人の体験の理解が深まり、より適切な介入や支援が導かれることが期待できる。

③DLB群 vs neurological control (DAT＋ND) 群におけるSDI-DLBのROC曲線



（文献3より）

④各群のSDI-DLB得点の分布



（文献3より）

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ORIGINAL ARTICLE

The impact of subjective memory complaints on quality of life in community-dwelling older adults

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Abstract

Purpose: The aim of this study was to evaluate the impact of memory complaints on quality of life (QOL) in elderly community dwellers with or without mild cognitive impairment (MCI).

Methods: Participants included 120 normal controls (NC) and 37 with MCI aged 65 and over. QOL was measured using the Japanese version of Satisfaction in Daily Life, and memory complaints were measured using a questionnaire consisting of four items. The relevance of QOL was evaluated with psychological factors of personality traits, sense of self-efficacy, depressive mood, self-evaluation of daily functioning, range of social activities (Life-Space Assessment), social network size, and cognitive functions including memory. The predictors of QOL were analyzed by multiple linear regression analysis.

Results: QOL was not significantly different between the NC and MCI groups. In both groups, QOL was positively correlated with self-efficacy, daily functioning, social network size, Life-Space Assessment, and the personality traits of extraversion and agreeableness; QOL was negatively correlated with memory complaints, depressive mood, and the personality trait of neuroticism. In regression analysis, memory complaints were a negative predictor of QOL in the MCI group, but not in the NC group. The partial correlation coefficient between QOL and memory complaints was –0.623 ($P < 0.05$), after scores of depressive mood and self-efficacy were controlled. Depressive mood was a common negative predictor in both groups. Positive predictors were Life-Space Assessment in the NC group and sense of self-efficacy in the MCI group.

Conclusions: Memory complaints exerted a negative impact on self-rated QOL in the MCI group, whereas a negative correlation was weak in the NC group. Memory training has been widely practised in individuals with MCI to prevent the development of dementia. However, such approaches inevitably identify their memory deficits and could aggravate their awareness of memory decline. Thus, it is critical to give sufficient consideration not to reduce QOL in the intervention for those with MCI.

INTRODUCTION

Even though many elderly people complain about diminishing memory function, not much attention has been given to the impact of memory complaints on quality of life (QOL).[1] Because enhancing QOL is regarded as one of the principal goals of management for all stages of dementia and its prodromal stages,[2,3] we investigated the impact of memory complaints on QOL in individuals with mild cognitive impairment (MCI) and in those without objective cognitive deficit.

As QOL is a multidimensional concept, socio-psychological factors, including depressive mood,[4,5] personality traits,[6] self-evaluation of remaining function for independent living, sense of self-efficacy, and social relationships, were taken into account as possible predictors of QOL.[7]

METHOD

Participants

Participants were recruited from community dwellers in Takasaki City, Japan; they agreed to participate in a 3-month programme for prevention of mental decline conducted by local municipalities between April 2010 and July 2010. Participants were required to be aged 65 and over.

Participants were screened using a questionnaire regarding cognitive status. Under the Preventive Long-Term Care Program in Japan, individuals at high risk for cognitive decline have been identified by a questionnaire. The municipalities were required by law to mail the questionnaire to inhabitants aged 65 and older. The questionnaire consists of 25 self-completed items including three items concerning mental decline: (i) Have others indicated that you may have memory problems (e.g. others saying that you often ask the same things repeatedly)?; (ii) Do you need to look up commonly used telephone numbers?; and (iii) Do you sometimes fail to remember the date? The dwellers were required to answer whether these incidents had occurred. The questionnaire was self-completed; thus, those lacking fluency in written or spoken Japanese were excluded. A total of 2387 residents answered yes to at least one of the three items in the four areas of Takasaki City, and 153 of them attended an orientation meeting. Also, at a community centre for the elderly, we recruited and obtained an additional 13 applicants. Written informed consent was obtained from 162 subjects. (Four subjects withdrew.) At the assessment, each subject completed the Mini-Mental State Examination (MMSE) and a medical interview by a specialist in dementia medicine. During the interview, five subjects were excluded who met the International Classification of Diseases 10 research criteria for the diagnosis of dementia.

We analyzed subjects who were diagnosed as suffering from MCI (n = 37) and controls with normal cognitive abilities (NC) (n = 120). MCI was diagnosed by a physician who specialized in dementia based on criteria from a report by the International Working Group on Mild Cognitive Impairment.[8] The questionnaire was completed at the baseline assessment of the intervention.[9]

This research was carried out in compliance with the Helsinki Declaration. The Ethics Board of Gunma University School of Health Sciences (Maebashi, Japan) approved all procedures (No. 21–47).

Measurement

Quality of life

QOL was measured using a self-rated questionnaire, the Japanese version of the Satisfaction in Daily Life (SDL).[10] The SDL is a simple measurement of 11 items: physical health, mental health, self-care, gait, housework, house facilities, partner and family relationships, hobby and leisure activities, social interaction, economic state and social security, and job satisfaction (including part-time or voluntary work and housekeeping jobs). Each item was rated on a scale of 1 to 5, with 'dissatisfied' rated as 1 and 'satisfied' rated as 5. Thus, the lowest total score could be 11 and the highest score could be 55. The mean ± SD SDL score was 44.2 ± 7.3 in individuals aged 60–69 years and 42.1 ± 8.7 in those aged 70–79 years.

Memory complaints

Memory complaints were assessed using the Questionnaire for Subjective Memory Complaint (Q-SMC),[11] which consisted of four questions: (i) Are there times when you are unable to remember what date it is even if you see a calendar?; (ii) Are there times when you forget where you placed your wallet or keys?; (iii) Are there times when you read something you had scheduled in your calendar or diary and are unable to recall what you had planned?; and (iv) Are there times when you are unable to remember what you heard 5 min ago? Each item was evaluated on a scale of 0 to 3, with 0 being 'never' and 3 being 'always'. The mean ± SD Q-SMC score was 5.59 ± 1.61 in individuals aged 74.1 ± 5.8 years (n = 95).[11]

Psychological factors

(1) Depressive mood. Depressive state was evaluated using the Japanese version of the Geriatric Depression Scale (GDS).[12] GDS is a 15-item, self-rated assessment that screens for depression in elderly populations. Scores of 0–4 indicate a lack of depressive tendency, 5–9 indicate a mild depressive tendency, and 10–15 indicate a severe depressive tendency.

(2) Sense of self-efficacy. Sense of self-efficacy was measured using the Japanese version of the General Self-Efficacy Scale (SE).[13] General self-efficacy is the belief in one's competence to cope with variable stressful or challenging demands, whereas specific self-efficacy is restricted to a specific demand. SE is designed to assess optimistic self-belief to cope with a variety of difficult demands in life. The mean ± SD SE was 77.30 ± 14.13 in men aged 65–74 years, 75.68 ± 13.96 in women aged 65–74 years, 71.86 ± 15.24 in men aged 75 years and over, and 72.37 ± 14.87 in women aged 75 and over.[14]

(3) Personality traits. Personality traits were assessed using the Big Five scale of personality traits.[15] The Big Five factors are extraversion, neuroticism, openness to experience, conscientiousness, and agreeableness. As the personality traits have sociocultural implication, we used the scale that was developed and validated in Japan.

Functional capacity for independent living

Functional capacity for independent living was assessed by the Tokyo Metropolitan Institute of Gerontology Index of Competence (TMIG-IC), which was designed to measure higher-level functional capacities in community-dwelling elderly residents who could not be adequately assessed by existing basic or instrumental activities of daily living scales.[16,17] TMIG-IC consists of 13 items on three subscales: instrumental self-maintenance, intellectual activity, and social role. The mean ± SD TMIG-IC was 10.8 ± 3.0 in individuals with a mean age of 72.5 years (n = 1809).[18]

Social factors

(1) Social network size. Social network size was assessed using the Japanese version of the abbreviated Lubben Social Network Scale,[19] which evaluates the size of a social network that is attributable to family ties and a parallel set attributable to friendship ties. The scores range from 0 to 30, and higher scores indicate larger social networks. In Japanese samples, the mean ± SD Lubben Social Network Scale score was 16.2 ± 5.1 in individuals aged 67.0 ± 6.8 years (n = 232).[20]

(2) Range of activity. The Life-Space Assessment (LSA) assessed a subject's range of activities based on how far and how often a person moves to each of the defined levels and any assistance needed to get to each level. LSA can assess the full range of mobility, ranging from mobility dependent on assistance from another person and limited to the room where a person sleeps daily, to travel out of the person's town independently during the month preceding the assessment.[21] The mean ± SD LSA was 91.6 ± 13.8 in individuals aged 74.0 ± 5.5 years (n = 321).[22]

Cognitive function

Cognitive function was measured by MMSE, and two subtests of the 5-Cog test were analyzed in the present study:[23] memory test (category-cued delayed recall test consisting of 32 words in eight categories) and executive function test (dual-task test requiring alternating attention). The mean ± SD scores in cognitively normal subjects (age range: 65–80 years; n = 800) were 12.0 ± 5.8 on the memory test and 20.1 ± 9.1 on the executive function test.

Physical factors

Aged individuals generally suffer from multiple diseases in various stages. Thus, it is difficult to obtain comprehensive information from a health questionnaire. Therefore, we did not include physical factors as variables. Instead, we established inclusion criteria, and participants were limited to those who could live independently in the community.

Analysis

We compared the SDL scores between the NC and MCI groups using a two-sample t-test. Pearson's correlation coefficients were obtained between the social-psychological-cognitive factors and the SDL score for each of the two groups. The factors with significant coefficients were entered in a stepwise manner into the multiple linear regression model as independent variables, with the SDL score as the dependent variable. Then, we obtained the partial correlation coefficient between the SDL score and each of the variables within the final model of multiple regression. The data were analyzed using the Japanese version of SPSS for Windows version 19.0 (IBM, Armonk, New York, USA) and level of statistical significance was set as $P < 0.05$.

RESULTS

Characteristics of subjects

Table 1 contains descriptive statistics for participants and the outcome variables. SDL scores were 44.3 ± 5.6 in the NC group and 44.2 ± 7.1 in the MCI group,

Table 1 Demographic data and correlation with quality of life (QOL)

Stage	NC (n = 120) (Men/women) (30/90)		MCI (n = 37) (Men/women) (17/20)		NC vs MCI
Gender	Mean ± SD	r†	Mean ± SD	r†	P-value‡
QOL (SDL)§	44.3 ± 5.6		44.2 ± 7.1		0.926
Age	71.9 ± 4.1	−0.183*	73.1 ± 4.4	0.261	0.127
Years of education	11.9 ± 2.2	−0.019	11.5 ± 3.0	0.067	0.372
Memory complaints (Q-SMC)§	6.3 ± 1.7	−0.211*	6.9 ± 2.2	−0.653***	0.082
Psychological factors					
Depressive mood (GDS)§	3.3 ± 3.0	−0.715***	4.1 ± 3.4	−0.550***	0.141
Self-efficacy (SE)§	76.7 ± 12.1	0.489***	74.0 ± 12.1	0.623***	0.245
Personality traits (Big Five)§					
Extraversion	51.0 ± 9.5	0.425***	51.1 ± 7.3	0.372*	0.946
Neuroticism	48.8 ± 9.4	−0.332***	49.8 ± 9.3	−0.439**	0.581
Intellect	48.5 ± 8.7	0.186*	49.7 ± 9.1	0.027	0.474
Conscientiousness	53.4 ± 8.3	0.099	49.9 ± 7.8	0.495**	<0.05
Agreeableness	56.2 ± 8.2	0.185*	53.0 ± 5.6	0.622***	<0.05
Cognitive function					
MMSE	28.4 ± 1.5	−0.082	25.7 ± 1.9	0.135	<0.001
Memory test	15.2 ± 4.5	0.038	8.8 ± 3.5	0.222	<0.001
Executive function test	21.9 ± 6.4	−0.055	14.7 ± 7.2	0.026	<0.001
Functional capacity					
TMIG-IC	12.0 ± 1.4	0.278**	11.7 ± 1.6	0.380*	0.302
Social factors					
Lubben social network size	16.8 ± 6.0	0.431***	16.5 ± 5.5	0.597***	0.810
Life-space assessment (LSA)§	90.8 ± 19.7	0.366***	96.3 ± 17.4	0.370*	0.128

*P < 0.05, **P < 0.001, ***P < 0.001. †Correlation coefficients with SDL, level of significance. ‡Comparison between scores of NC and MCI by two sample t-test. §Related test appears in parentheses. GDS, the Japanese version of Geriatric Depression Scale; LSA, Life-Space Assessment; Lubben, the Japanese version of the abbreviated Lubben Social Network Scale; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; NC, normal controls; Q-SMC, the Questionnaire for Subjective Memory Complaint; SDL, Satisfaction in Daily Life; SE, the Japanese version of the General Self-Efficacy scale; TMIG-IC, Tokyo Metropolitan Institute of Gerontology Index of Competence.

and were not significantly different between the NC and MCI groups (P = 0.926).

Possible QOL predictors

The factors showing significant correlation with SDL scores were similar in the NC and MCI groups, with the exception of personality traits (Table 1). There were positive correlations between SDL scores and self-evaluation scores of remaining function (i.e. sense of self-efficacy and daily functioning (TMIG-IC)), social factors of social network size (Lubben Social Network Scale), and range of activity (LSA). A negative correlation was observed between SDL scores and both scores related to memory complaints (Q-SMC) and depressive mood (GDS).

No significant correlation was observed between SDL scores and either cognitive scores (MMSE, memory test and executive function test) or years of education (Table 1).

There was also no correlation between memory complaints (Q-SMC) and MMSE (NC: r = −0.082; MCI: r = 0.135), memory function (NC: r = 0.038; MCI: r = 0.222), or executive function (NC: r = −0.055; MCI: r = 0.026). The gender difference on the SDL was not significant in either the NC or MCI group.

QOL predictors after controlling for other factors

There were several independent variables in the final models of the stepwise multiple regression analyses for the NC and MCI groups. Memory complaint (Q-SMC) was a negative predictor in the MCI group. The positive predictors were range of activity (LSA) in the NC group and sense of self-efficacy (SE) in the MCI group. Depressive mood (GDS) was a common negative predictor in both groups (Table 2). The partial correlation coefficient between the SDL and Q-SMC scores in the MCI group was −0.62 (P < 0.001), when the SE and GDS scores were controlled. In the same way, the coefficient between the SDL and GDS scores was −0.51 (P < 0.01) after the SE and Q-SMC scores were controlled. The coefficient between the SDL and SE scores was −0.37 (P < 0.05) after the GDS and

Table 2 Regression models of factors predicting QOL score

A. NC group

Predictors	Unstandardized β	Unstandardized SD	Standardized β	*t*-value	*P*-value
(Constant)	43.912	2.190		20.051	<0.001
GDS	−1.251	0.133	−0.662	−9.389	<0.001
LSA	0.051	0.021	0.168	2.380	<0.05

B. MCI group

Predictors	Unstandardized β	Unstandardized SD	Standardized β	*t*-value	*P*-value
(Constant)	45.557	6.728		6.771	<0.001
Q-SMC	−1.439	0.319	−0.490	−4.506	<0.001
GDS	−0.757	0.225	−0.374	−3.369	<0.01
SE	0.156	0.070	0.268	2.233	<0.05

GDS, the Japanese version of Geriatric Depression Scale; LSA, Life-Space Assessment; MCI, mild cognitive impairment; NC, normal controls; Q-SMC, the Questionnaire for Subjective Memory Complaint; SE, the Japanese version of the General Self-Efficacy scale.

Q-SMC scores were controlled. In the NC group, the partial correlation coefficient between the QOL and GDS scores was −0.67 ($P < 0.001$) after the LSA scores were controlled, whereas the coefficient between the QOL and LSA scores was not significant ($r = 0.17$) after the GDS scores were controlled.

DISCUSSION

Memory complaints had a negative impact on self-rated QOL in the MCI group, whereas a negative correlation was weak in the NC group. The QOL scores did not significantly correlate with the memory test in either the MCI or NC group. In multiple linear regression analysis, subjective memory complaint was found to be a negative predictor of QOL. This was further confirmed by partial correlation analysis. The QOL scores were significantly correlated with the scores of subjective memory complaints after the scores of self-efficacy and depressive mood were controlled.

These results suggest that those with MCI consider their awareness of memory decline seriously enough to affect their QOL. When self-awareness of memory decline is considered, it should be taken into account whether one can evaluate one's own memory function properly. Deterioration of self-awareness of memory decline is characteristic of patients with Alzheimer's disease and other types of dementia. Individuals with dementia tend to overestimate their capacity and ignore their deficits,[24] whereas those with MCI retain the ability to estimate their own memory function in most cases.[25] Consequently, those with MCI may recognize that their own memory decline is more severe than age-related decline, and they are all the more afflicted with fear of developing dementia.

Depressive state was a negative predictor in the MCI group. It is well established that QOL is intrinsically related to depressive mood,[26–28] which is also highly associated with the personality trait of neuroticism among elderly individuals.[29,30]

With regard to positive predictors, sense of self-efficacy was shown to be a positive predictor of self-rated QOL in the MCI group. A higher sense of self-efficacy was reported as a positive predictor of QOL in demented individuals.[31] As autonomy becomes limited among those with MCI, they are confronted by limits in their social lives. Thus, a higher sense of self-efficacy would contribute to higher life satisfaction.

For those with MCI, an approach that aims to improve memory function could soothe the fear of memory decline, and cognitive stimulation, including memory training, has been widely practised in individuals with MCI to prevent the development of dementia. However, it should be noted that such approaches inevitably identify what those with MCI are incapable of doing and could aggravate their awareness of memory decline. The fear of developing dementia and the realization of their memory deficits can devastate the self-confidence of those with MCI and worsen their depressive tendency. Indeed, adverse effects of cognitive training, such as frustration, anxiety, depression, and reduced self-esteem, have been reported,[32,33] and the consensus statement of the American Association for Geriatric Psychiatry warned of the potentially harmful effects of cognitive training.[34] Thus, cognitive training should be conducted with full attention to the mental state of the individual, so as to avoid exacerbating his or her depressive state or damaging his or her sense of self-efficacy for the improvement of QOL.

Limitations

With regard to limitations, the questionnaires used in the study, including QOL, depressive mood, and personality assessments, were self-rated, and it is necessary to confirm the results using a more objective evaluation of QOL. Additionally, those in the NC group in this study subjectively perceived cognitive decline, although they showed no objective cognitive decline.

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The authors have no conflicts of interest to report.

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ORIGINAL ARTICLE

CSF levels of Aβ1-38/Aβ1-40/Aβ1-42 and ^{11}C PiB-PET studies in three clinical variants of primary progressive aphasia and Alzheimer's disease

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Abstract

Primary progressive aphasia (PPA) is a cognitive syndrome characterized by progressive and isolated language impairments due to neurodegenerative diseases. Recently, an international group of experts published a Consensus Classification of the three PPA clinical variants (naPPA, svPPA and lvPPA). We analyzed 24 patients with PPA by cognitive functions, neuroimaging (MRI, ^{99m}Tc ECD-SPECT, ^{11}C PiB-PET and FDG-PET) and cerebrospinal fluid (CSF) analysis (ptau-181, Aβ1-42, Aβ1-40 and Aβ1-38), to elucidate relationships between neuroimaging studies and biochemical findings in the three PPA clinical variants. Cognitive and speech functions were measured by mini-mental state examination and standard language test of aphasia. The patients with lvPPA showed significant decreases in CSF Aβ1-42 and ratios of Aβ1-42/Aβ1-40 and Aβ1-42/Aβ1-38, and significant increases in CSF ptau-181 and ratios of ptau-181/Aβ1-42 and ptau-181/Aβ1-38; these findings were similar to those of patients with Alzheimer's disease (AD). We observed a higher frequency of the ApoE ε4 allele in the lvPPA patients relative to the two other PPA variants. In ^{11}C PiB-PET of lvPPA patients, PiB positive findings were detected in cortices of frontal, temporal and parietal lobes and the posterior cingulate, where massive Aβ may accumulate due to AD. Our results of AD-CSF markers including Aβ1-38 and ^{11}C PiB-PET in the lvPPA patients demonstrate a common pathological mechanism with the occurrence of AD.

Abbreviations: Aβ: β amyloid β protein; AD: Alzheimer's disease; AOO: age of onset; AOS: apraxia of speech; Apo E: apolipoprotein E; ^{11}C PiB-PET: ^{11}C Pittsburgh compound B-positron emission tomography; ^{11}C PBB3-PET: ^{11}C Pyridinyl-Butadienyl-Benzothiazole-positron emission tomography; CSF: cerebrospinal fluid; ELISA: enzyme-linked immunosorbent assay; EOSAD: early-onset sporadic AD; FDG-PET: ^{18}F-fluorodeoxy glucose-positron emission tomography; FTD: frontotemporal dementia; FTLD: frontotemporal lobar degeneration; ^{123}I IMP-SPECT: N-isopropyl-p-(iodine-123)-iodoamphetamine; LOSAD: late-onset sporadic AD; lvPPA: logopenic variant PPA; MMSE: mini-mental state examination; naPPA: non-fluent/agrammatic variant PPA; ND: non-demented subject; PCA: posterior cortical atrophy; PPA: primary progressive aphasia; ptau: phosphorylated tau; S.D.: standard deviation; SLTA: Standard Language Test of Aphasia; svPPA: semantic variant PPA; ^{99m}Tc-ECD SPECT: ^{99m}Tc-ethyl cysteinate dimer single photon emission computerized tomography.

Keywords

^{11}C PiB-PET, amyloid β protein, Alzheimer's disease, cerebrospinal fluid, primary progressive aphasia

History

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Introduction

Primary progressive aphasia (PPA) is a cognitive syndrome characterized by a progressive and initially isolated language impairment caused by a neurodegenerative disease [1]. The non-fluent/agrammatic variant of PPA (naPPA) is characterized by agrammatism and/or motor speech articulatory errors due to an apraxia of speech (AOS), in which impairment of sentence comprehension for difficult syntactic constructions may also be present [2,3]. The core features of the semantic variant of PPA (svPPA) are impaired confrontation naming and single-word comprehension [4], while object knowledge

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is usually affected but repetition and motor speech are spared. The consensus neuroimaging markers for naPPA are atrophy and/or functional abnormalities in the left posterior fronto-insular region [2,3]. A consensus meeting developed criteria for these conditions in relation to frontotemporal lobar degeneration (FTLD) [5]. Later, other affected cognitive domains and different accompanying language disorders were recognized. The logopenic variant of PPA (lvPPA) was defined by hesitant speech with word-finding pauses due to impaired single-word retrieval and difficulty in sentence repetition, without object knowledge and motor deficits of speech [6]. For lvPPA, the MRI findings are predominant in left posterior perisylvian or parietal atrophies [6]. Consequently, functional neuroimaging studies have established consistent neuroanatomical correlations in three clinical variants of PPA [7–9]. According to these defining characteristics, an international group of experts published a Consensus Classification of the most accepted three clinical variants of PPA (naPPA, svPPA, lvPPA) [10]. In the last decade, cerebrospinal fluid (CSF) biomarkers [11] and amyloid positron emission tomography (^{11}C PiB-PET) [12,13] have been developed in research settings to elucidate clinical–pathological correlations of Alzheimer's disease (AD). So far, some subgroup of patients with PPA have high association with the CSF diagnostic AD markers [14,15], and the neuroimaging biomarkers of amyloid PET/FDG-PET [7,8,16,17] and MRI [8,9,18].

Materials and methods

Subjects

This study complied with the Declaration of Helsinki and was approved by the Institutional Review Boards (IRB) of Gunma University Graduate School of Medicine, Geriatrics Research Institute and Hospital, and Maebashi Red Cross Hospital. The spouse or family members of each AD patient provided written informed consent for the patient to participate in the study. The subjects who underwent lumbar punctures were recruited at Gunma University Graduate School of Medicine, Geriatrics Research Institute and Hospital, and Maebashi Red Cross Hospital (Maebashi, Gunma, Japan). Upon entering the study, subjects underwent a standardized clinical assessment, including medical history, physical and neurological examinations, Mini-Mental State Examination (MMSE) [19], brain MRI and/or computed tomography (CT) scan. AD was diagnosed for patients scoring 23 points or fewer on the MMSE [20], combined with caregivers' information of patients' daily activities. Diagnostic criteria of the National Institute of Neurological and Communicative Diseases and Stroke-Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) [21] were used for AD diagnosis. Subjects were classified as non-demented (ND) if they scored more than 24 points on the MMSE, and if, based upon information on activities of daily living (ADL) provided by the family, they were considered to have a normal daily life not requiring any intellectual assistance. Speech function of patients was estimated by the Standard Language Test of Aphasia (SLTA) [22,23]. SLTA is a test battery originally developed for language function to estimate multi-domains, including "Confrontation naming", "Word repetition", "Sentence repetition", "Auditory single-word comprehension", and "Auditory complex sentence comprehension commands". Three variants of PPA patients were diagnosed clinically, based on the Consensus Classification of the three most accepted PPA clinical variants [10].

Demographics of PPA patients and AD

The number of patients in each study group was as follows: 10 for naPPA, 4 for svPPA, 10 for lvPPA, and 50 for AD patients. Age of onset (AOO, years old, mean ± SD) was 63.50 ± 5.06 in naPPA patients, 62.00 ± 0.82 in svPPA patients, 64.70 ± 4.97 in lvPPA patients and 64.8 ± 8.01 in AD patients. Duration of the disease (years) was 5.60 ± 1.78 in naPPA patients, 4.00 ± 1.83 in svPPA patients, 4.00 ± 1.16 in lvPPA patients and 3.06 ± 1.99 in AD patients. The male ratio to total patient number was 0.50 in naPPA patients, 1.00 in svPPA, 0.50 in lvPPA patients and 0.40 in AD patients. The years of attained education were 11.70 ± 0.95 for naPPA patients, 13.00 ± 2.00 for svPPA patients, 12.10 ± 1.66 for lvPPA patients and 12.25 ± 2.13 in AD patients.

Neuroimaging studies

MRI or CT scan, ^{99m}Tc ECD-SPECT and ^{11}C PiB-PET and FDG-PET neuroimaging studies were performed for the patient study groups. Each MRI and SPECT/PET scan was evaluated by an experienced radiologist or nuclear medicine clinician and two neurologists; all evaluators were blinded to the patients' data on neurological findings, cognition and linguistic assessment (MMSE and SLTA). For each patient in the PPA variant and AD study groups, we assessed the presence or absence of imaging-supported diagnostic biomarkers by MRI, SPECT and FDG-PET [7–10,16–18]: (A) predominant atrophy and/or hypoperfusion/hypometabolism in the left posterior fronto-insular region (naPPA), (B) predominant atrophy and hypoperfusion/hypometabolism in the left anterior temporal lobe (svPPA), (C) predominant atrophy and hypoperfusion/hypometabolism in the left posterior perisylvian or parietal region (lvPPA), (D) hypoperfusion/hypometabolism in bilateral posterior cingulate gyrus and precuneus (AD) (Figure 1A–D).

PiB (2-(4-aminophenyl)-6-hydroxybenzothiazole) was synthesized for ^{11}C PiB-Positron Emission Tomography (^{11}C PiB-PET) [12]. After an intravenous injection of ^{11}C-PiB (550 MBq), a dynamic 70-min scan was acquired in the three-dimensional mode without arterial sampling using an Eminence-B PET scanner (General Electric, CT, USA). CT scans were co-registered with the respective PET images using the PMOD image-fusion tool (PMOD Technologies Ltd., Zurich, Switzerland). The PET images were reconstructed using a filtered back-projection algorithm for attenuation and scatter corrections. According to a previous study [24], in which the frame summation of the dynamic images was recorded for 70 min, Logan graphical analysis was used for determining the regional counts (SUVR)(distribution volume ratio, DVR = binding potential + 1) using the cerebellum as the reference region. For this purpose, the cortical lesions occurring in the frontal and temporal lobes and posterior cingulate gyrus were selected. The mean cortical DVR (MCDVR) was the mean of the DVR values

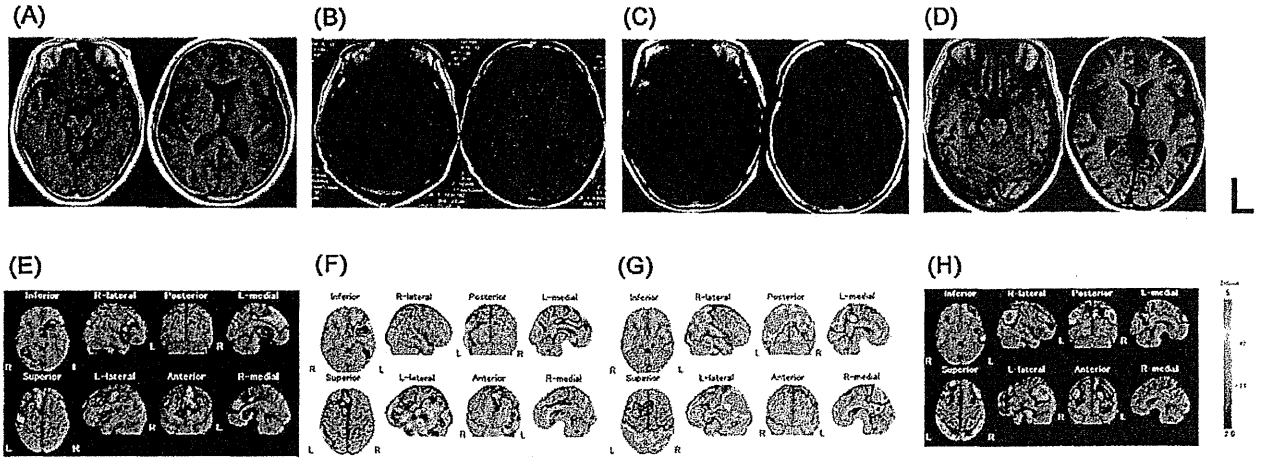

Figure 1. MRI and ^{99m}Tc ECD-SPECT.Brain MRI of PPA patients for naPPA (A), lvPPA (B), svPPA (C) and early-onset AD (D). ^{99m}Tc ECD-SPECT of patients for naPPA (E), lvPPA (F), svPPA (G) and AD (H). naPPA is characterized by predominant atrophy (A) and hypoperfusion (E) in the left posterior fronto-insular region, svPPA by predominant atrophy (B) and hypoperfusion in the left anterior temporal lobe (F), and lvPPA by predominant atrophy (C) and hypoperfusion in the left posterior perisylvian or parietal region (G). An early-onset AD patient showed frontal and temporal lobes atrophy (D), and hypoperfusion in the frontal lobes and parietal lobes cortices and the posterior cingulate (H).

of these lesions. Positive ^{11}C PiB binding indicated that the visible cortical ^{11}C PiB accumulation was higher than that of the white matter or that the MCDVR of the cortex was larger than the cutoff index obtained at our hospital.

CSF biomarkers

Measurement of CSF Aβ1-42, Aβ1-40 and Aβ1-38

CSF was obtained by a lumbar puncture in the L3/L4 or L4/L5 intervertebral space. CSF samples were centrifuged for 10 min at 1800 *g* at 4 °C within 3 h of collection. Samples were divided into aliquots of 0.5 mL in polypropylene tubes and stored at −80 °C until analysis using an ELISA kit for human CSF Aβ1-40 (Wako Pure Chemical Industries, Tokyo, Japan), human CSF Aβ1-42 (Wako Pure Chemical Industries) and human CSF Aβ1-38 (IBL, Gunma, Japan) [25,26].

Measurement of CSF phosphorylated tau 181

Measurement of ptau-181 in CSF was performed by sandwich ELISA (Innogenetics, Ghent, Belgium) as described elsewhere [27].

Genetic analysis of apolipoprotein E

After obtaining informed consent for genetic testing, we purified genomic DNA from lymphocytes in the peripheral blood of affected subjects. For the analysis of apolipoprotein E genotype, purified genomic DNA was examined as previously described [28].

Results

Mini-mental state examination

Scores (full score 30: mean ± S.D.) of mini-mental state examination (MMSE) were 17.20 ± 7.47 in naPPA patients, 6.75 ± 5.56 in svPPA patients, 15.70 ± 4.92 in lvPPA patients and 18.44 ± 4.74 in AD patients. The MMSE score for svPPA patients was lower than those of naPPA and lvPPA patients ($p < 0.0001$, respectively (Table 1).

Standard Language Test of Aphasia

Scores for "Naming" (% correct: mean ± S.D.) from the Standard Language Test of Aphasia (SLTA) were 39.00 ± 19.26 in naPPA patients, 16.25 ± 4.79 in svPPA patients and 59.00 ± 21.58 in lvPPA patients. Scores for "Single-word repetition" (% correct) from the SLTA were 76.00 ± 18.38 in naPPA patients, 75.00 ± 19.15 in svPPA patients and 75.00 ± 23.21 in lvPPA patients. Scores for "Sentence repetition" (% correct) from the SLTA were 30.0 ± 17.00 in naPPA patients, 40.00 ± 43.20 in svPPA patients and 32.00 ± 19.32 in lvPPA patients. Scores for "Auditory single-word comprehension" (% correct) from the SLTA were 76.00 ± 22.71 in naPPA patients, 42.50 ± 38.62 in svPPA patients and 77.00 ± 22.14 in lvPPA patients. Scores for "Auditory sentence comprehension command" (% correct) from the SLTA were 66.00 ± 28.75 in naPPA patients, 15.00 ± 10.00 in svPPA patients and 58.00 ± 30.48 in lvPPA patients. The scores for "Naming" and "Single-word comprehension" in svPPA patients were significantly lower than those of naPPA and lvPPA patients (*$p < 0.001$, **$p < 0.0001$, Mann–Whitney test, Table 1), while the scores for "Auditory single-word comprehension" and "Auditory sentence comprehension command" in svPPA patients were significantly lower than those of naPPA and lvPPA patients (**$p < 0.0001$, Mann–Whitney test, Table 1). The scores for "Calculation" in lvPPA patients were significantly lower than those for naPPA and svPPA patients (**$p < 0.0001$, Mann–Whitney test, Table 1).

Neuroimaging (MRI, ^{99m}Tc ECD-SPECT, FDG-PET and ^{11}C PiB-PET)

The 24 PPA patients were clinically subclassified into 10 naPPA patients, 4 svPPA patients and 10 lvPPA patients according to the Consensus classification of PPA [10]. All the

Table 1. Summary of clinical features, MMSE and SLTA for the 24 PPA patients.

	naPPA ($N=10$)	svPPA ($N=4$)	lvPPA ($N=10$)
Clinical information			
Age of onset (year)	63.50 ± 5.06	62.00 ± 0.82	64.70 ± 4.97
Disease duration (years)	5.60 ± 1.78	4.00 ± 1.83	4.00 ± 1.16
Male gender (%)	50	100	50
Education (years)	11.70 ± 0.95	13.00 ± 2.00	12.10 ± 1.66
MMSE	17.20 ± 7.47	6.75 ± 5.56**	15.70 ± 4.92
SLTA			
Naming (% correct)	39.00 ± 19.26*	16.25 ± 4.79**	59.00 ± 21.58
Single-word repetition (% correct)	76.00 ± 18.38	75.00 ± 19.15	75.00 ± 23.21
Sentence repetition (% correct)	30.00 ± 17.00	40.00 ± 43.20	32.00 ± 19.32
Auditory single-word comprehension (% correct)	76.00 ± 22.71	42.50 ± 38.62**	77.00 ± 22.14
Auditory sentence comprehension (% correct)	66.00 ± 28.75	15.00 ± 10.00**	58.00 ± 30.48
Calculation (% correct)	41.00 ± 27.67	40.00 ± 46.19	28.50 ± 27.79**

Figures indicate means ± SD or number with percentages in parentheses. MMSE = mini-mental state examination; SLTA = standard language test of aphasia. Asterisks denote significantly impaired at $*p<0.001$ and $**p<0.0001$ (Mann–Whitney test).

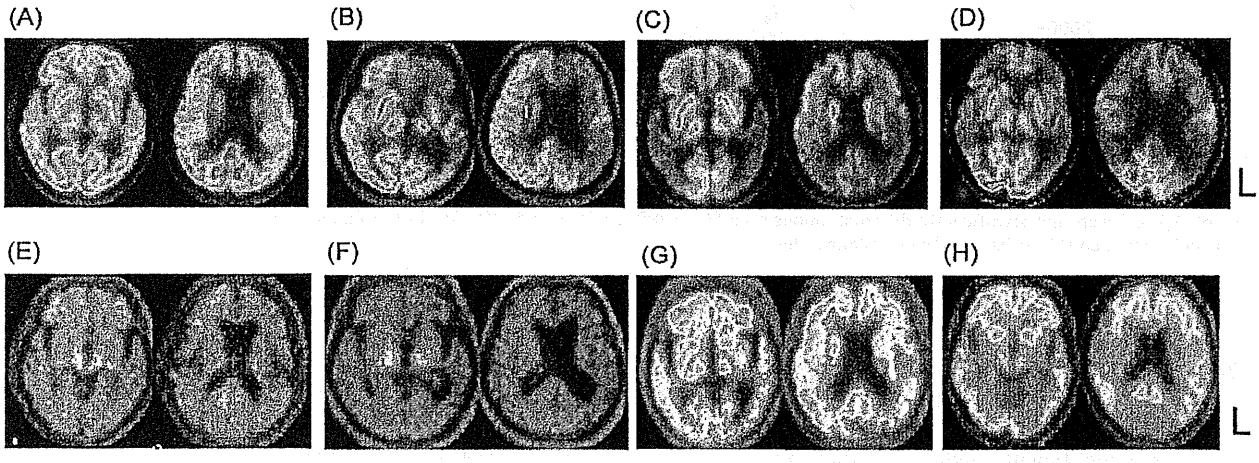

Figure 2. FDG-PET and ^{11}C PiB-PET. (A) In naPPA patients, FDG-PET analysis showed glucose hypometabolism in the left posterior fronto-insular region. (B) ^{11}C PiB-PET showed no abnormal signal lesion in the brain of naPPA patients. (C) In svPPA patients, FDG-PET showed glucose hypometabolism in the left anterior temporal lobe, while no PiB positive signal finding in cerebral cortices (D). (E) While lvPPA patients showed glucose hypometabolism in the left anterior temporal lobe by FDG-PET, ^{11}C PiB-PET showed abnormal high PiB signal findings in cerebral cortices of frontal lobes and temporal lobes and the posterior cingulate (F). (G) An early-onset AD patient showed glucose hypometabolism in bilateral frontal and temporal lobes, presenting abnormal PiB positive signal findings in cerebral cortices and the posterior cingulate in ^{11}C PiB-PET (H).

10 naPPA patients showed brain atrophy in the left posterior fronto-insular region by MRI (Figure 1A: a naPPA case). All the 10 naPPA patients showed hypoperfusion in the left posterior fronto-insular region by ^{99m}Tc ECD-SPECT (Figure 1E: a naPPA case). All the 4 svPPA patients showed atrophy in the left anterior temporal lobe by MRI or CT (Figure 1B: a svPPA case), and ^{99m}Tc ECD-SPECT showed hypoperfusion in the left anterior temporal lobe (Figure 1F: a svPPA case). All the 10 lvPPA patients showed brain atrophy in the left posterior perisylvian and parietal region by MRI or CT (Figure 1C: an lvPPA case) and hypoperfusion in the corresponding lesions by ^{99m}Tc ECD-SPECT (Figure 1G: an lvPPA case). An early-onset AD patient showed bilateral atrophy in the temporal and parietal lobes (Figure 1D), with bilateral hypoperfusion in the temporal and parietal lobes (Figure 1H).

All 7 naPPA patients showed glucose hypometabolism in the left posterior fronto-insular region by FDG-PET (Figure 2A). All 7 naPPA patients showed no abnormal signal lesion by ^{11}C PiB-PET (Figure 2E). All 4 svPPA patients showed glucose hypometabolism in the left anterior temporal lobe by FDG-PET (Figure 2B), while no PiB positive signal was found in the cerebral cortices (Figure 2 F). All 6 lvPPA patients showed glucose hypometabolism in the left anterior temporal lobe by FDG-PET (Figure 2C), and by ^{11}C PiB-PET showed PiB positive signal findings corresponding to Aβ accumulation bilaterally in the cerebral cortices (Figure 2G). By FDG-PET, an early-onset AD patient showed bilateral glucose hypometabolism in the frontal and temporal lobes (Figure 2D), and by ^{11}C PiB-PET presented bilateral PiB positive signal findings in the cerebral cortices of the frontal and temporal lobes, and also in the posterior cingulate (Figure 2H).

Comparative analysis of CSF data

The lvPPA patients showed lower levels of CSF Aβ1-42 and higher levels of CSF ptau-181 than ND. The CSF levels of ptau-181 (mean ± SD) were 33.59 ± 16.09 for naPPA ($N=10$), 42.24 ± 21.26 for svPPA ($N=4$), and

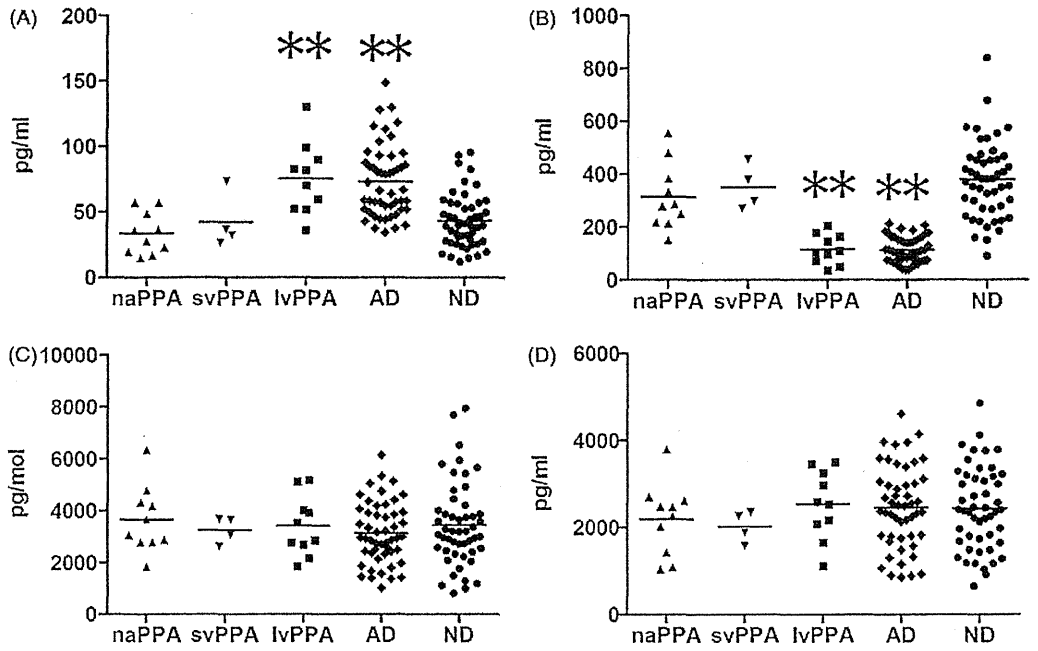

Figure 3. CSF levels of ptau-181, Aβ1-42, Aβ1-40 and Aβ1-38. (A) CSF levels of ptau-181 of lvPPA and AD showed significant increases compared to those of naPPA, svPPA and ND (**$p<0.0001$). (B) CSF levels of Aβ1-42 of lvPPA and AD showed significant decreases compared to those of naPPA, svPPA and ND (**$p<0.0001$). (C) CSF levels of Aβ1-40 were not significantly different amongst naPPA, svPPA, lvPPA and ND. (D) CSF levels of Aβ1-38 were not significantly different amongst naPPA, svPPA, lvPPA and ND. Bar in the Figure shows average data. Asterisks denote significantly impaired (**$p<0.0001$, Mann–Whitney test).

75.38 ± 27.32 for lvPPA ($N = 10$), 73.14 ± 27.26 for AD ($N = 50$) and 43.19 ± 20.49 for non-demented subjects ($N = 50$) (Figure 3A). The CSF levels of ptau-181 for lvPPA and AD were significantly higher than those for naPPA and svPPA (Figure 3A). No abnormal findings for naPPA and svPPA patients were observed in the CSF levels of Aβ1-42, Aβ1-40, Aβ1-38 or ptau-181. In the CSF levels of Aβ1-42, average scores were 314.42 ± 125.83 for naPPA, 351.35 ± 84.21 for svPPA, 115.98 ± 56.46 for lvPPA, 113.82 ± 48.84 for AD and 379.25 ± 144.45 for ND (Figure 3B). The CSF levels of Aβ1-42 for lvPPA and AD were significantly lower than those for naPPA, svPPA and ND (Figure 3B). In the CSF levels of Aβ1-40, average scores were 3647.09 ± 1293.76 for naPPA, 3248.58 ± 504.53 for svPPA, and 3401.29 ± 1151.24 for lvPPA, 3126.24 ± 1185.32 for AD and 3439.24 ± 1611.39 for non-demented subjects (Figure 3C). In the CSF levels of Aβ1-38, average scores were 2190.12 ± 839.47 for naPPA, 2023.82 ± 356.92 for svPPA, and 2535.66 ± 790.99 for lvPPA, 2464.03 ± 946.80 for AD and 2435.37 ± 950.67 for non-demented subjects (Figure 3D). In either CSF levels of Aβ1-38 or Aβ1-40, no significant difference was observed amongst naPPA, svPPA and lvPPA patients (Figure 3C and D).

Ratios of CSF Aβ molecules (Aβ1-42, Aβ1-40 and Aβ1-38) and ptau-181

The ratio of Aβ1-42/Aβ1-40 (mean ± S.D.) was 0.09 ± 0.04 for naPPA, 0.11 ± 0.02 for svPPA, 0.04 ± 0.02 for lvPPA, 0.05 ± 0.04 for AD and 0.14 ± 0.11 for ND. The ratios of Aβ1-42/Aβ1-40 for lvPPA and AD were significantly lower than those for naPPA, svPPA and ND (**$p<0.0001$, respectively, Figure 4A). The ratio of Aβ1-42/Aβ1-38 was 0.16 ± 0.06 for naPPA, 0.17 ± 0.01 for svPPA, 0.05 ± 0.01 for lvPPA, 0.06 ± 0.04 for AD and 6.92 ± 3.37 for ND. The ratios of Aβ1-42/Aβ1-38 for lvPPA and AD were lower than those of those for naPPA, svPPA and ND (**$p<0.0001$, respectively, Figure 4B). The ratio of Aβ1-38/Aβ1-40 was 0.641 ± 0.273 naPPA, 0.64 ± 0.12 for svPPA, 0.81 ± 0.34 for lvPPA, 0.94 ± 0.62 for AD and 0.95 ± 0.92 for ND. No significant difference was observed among these ratios for naPPA, svPPA, lvPPA, AD and ND (data not shown). The ratio of ptau-181/Aβ1-42 was 0.12 ± 0.07 for naPPA, 0.12 ± 0.03 for svPPA, 0.83 ± 0.50 for lvPPA, 0.79 ± 0.54 for AD and 0.14 ± 0.13 for ND. The results of ptau-181/Aβ1-42 for lvPPA and AD were significantly higher than those for naPPA, svPPA and ND (**$p<0.0001$, respectively, Figure 4C). The ratio of ptau-181/Aβ1-38 was 0.02 ± 0.01 for naPPA, 0.02 ± 0.01 for svPPA, 0.03 ± 0.02 for lvPPA, 0.04 ± 0.03 for AD and 0.02 ± 0.01 for ND. The results of ptau-181/Aβ1-38 for lvPPA and AD were significantly higher than those for naPPA, svPPA and ND (**$p<0.0001$, respectively, Figure 4D). The results of Aβ1-42/Aβ1-40, Aβ1-42/Aβ1-38, ptau-181/Aβ1-42 and ptau-181/Aβ1-38 for AD and lvPPA were quite similar to those for EOSAD/LOSAD and ND in previous study [26].

Apolipoprotein E genotypes

The apoE ε4 allele frequency in the patient groups was 0.05 in naPPA, 0 in svPPA and 0.40 in lvPPA. In this study, the frequency of the ApoE ε4 allele in lvPPA is quite similar to