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〈短　報〉

高齢者の耳掃除と高齢者総合的機能評価（Comprehensive Geriatric Assessment：CGA）との関係

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要　約　本研究の目的は，高齢者の耳掃除の実態を調査し，CGAとの関係を検討することである．当院もの忘れセンターの外来患者116名を対象に耳掃除の有無，認知機能，基本的ADL，抑うつ，意欲，周辺症状，介護負担について調査した．その結果，28％の患者が1年以上耳掃除をしておらず，耳掃除をしていない患者は耳掃除をしている患者よりも認知機能，基本的ADL，意欲，周辺症状が有意に低下もしくは悪化していた．

Key words：耳掃除，高齢者総合的機能評価（Comprehensive Geriatric Assessment：CGA）

（日老医誌　2013；50：264-265）

背　景

高齢者の聴力障害は，認知機能障害の要因となり[1)]認知症になるリスクが高い[2)]ことが明らかになっている．また高齢になると清潔に対する意識や意欲が低下するため，耳掃除をしなくなる高齢者が多い．

当院もの忘れセンターでも，5年にわたって耳掃除をしていなかったため難聴になっていた高齢者が，耳鼻科で耳垢を除去したところ，聴力の回復を自覚し，耳垢除去前には6点だったMini-Mental State Examination（MMSE）の点数が半年後には11点へと改善した症例を経験した．

我が国では，高齢者の耳垢除去の頻度と認知機能，聴力との関連を検討した論文は1編あるのみであり，耳垢がある高齢者はない高齢者に比べて，平均聴力が低く，MMSE得点も低いことが報告されている[3)]．そこで本研究は，高齢者の耳掃除の実態を調査し，認知機能を含むCGAとの関係について検討した．

Ear cleaning and Comprehensive Geriatric Assessment in Japanese elderly
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方　法

当院もの忘れセンターの外来患者116名（男性36名，女性80名，平均年齢80.1±5.8歳）を対象とした．MMSEの平均点は21.1±5.3点であった．

耳掃除の有無については，家族同伴のもと個別に口頭で確認した．なお本研究では，本人以外の者が行っている場合でも耳掃除有りとした．併せて，認知機能（MMSE），基本的ADL（Barthel Index；BI），抑うつ（Geriatric Depression Scale；GDS），意欲（Vitality Index；VI），周辺症状（Dementia Behavior Disturbance Scale；DBD），介護負担（Zarit Burden Interview；ZBI）についても評価した．

結　果

1．耳掃除の有無と頻度

33名が1年以上耳掃除をしていなかった（無群）．耳掃除をしている人（有群）の頻度は，数日おき14％，数週間おき37％，数カ月おき21％であった．また，在宅の場合は居住形態（独居，夫婦のみ，子どもと同居）に関わらず約30％が耳掃除をしておらず，入所の場合は50％がしていなかった．

2．耳掃除とCGAとの関係

耳掃除をしていない患者は耳掃除をしている患者よりもMMSEが有意に低下していた（有群21.9±5.2，無群19.1±5.2；$p=0.01$）．またBI（有群95.8±9.9，無群89.3±16.5；$p<0.01$），VI（有群9.4±0.9，無群8.7±1.6；$p<$

0.01），DBD（有群 16.9±10.8，無群 21.9±11.4；p＝0.03）も有意に低下もしくは悪化していた．項目別にみると，BIではトイレ動作や入浴，排便，排尿，VIでは起床意欲，コミュニケーション意欲，食欲，DBDでは日常的な物事への関心，適切な服装を選べない，失禁，食物を投げる，以上の項目で有意な差がみられた．GDSとZBIに有意な差はみられなかった．

考　察

もの忘れセンターに訪れる外来患者の28％が1年以上耳掃除をしていない実態が判明した．中でも，施設入所している患者は半数が耳掃除をしていなかった．欧米では入所している高齢者の34％に耳垢がたまっているという報告があるが[4]，これと比較しても，日本の施設では耳掃除が口腔ケアや爪切りなどのケアに比べて優先度の高いケアとして認識されていない可能性がある．

また耳掃除をしている患者に比べて，耳掃除をしていない患者の認知機能，基本的ADL，意欲，周辺症状は有意に低下もしくは悪化していた．杉浦らは，認知機能低下による清潔への関心の低下が耳垢栓塞を起こしやすくし，耳垢栓塞による聴力低下がコミュニケーション能力を低下させ，それがさらに認知機能を悪くするという悪循環の可能性を指摘している[3]が，本研究もこれを支持する結果であった．さらに耳掃除をしていない患者は，コミュニケーションだけでなく，起床や食事，更衣を含むセルフケアなどに対する様々な意欲の低下に加え，実際に入浴や排泄などの基本的な日常生活動作能力も低下していることが推測できる結果だった．

しかしながら，本研究は横断的調査であることに加え，聴力の測定も行っておらず，耳掃除と聴力，CGAとの因果関係には言及できない．今後は耳垢除去の介入研究を行い，耳垢栓塞と聴力，意欲，認知機能の関係を縦断的に検討することが必要である．

また，日本人の耳垢は欧米人と異なり，その多くが乾性で耳垢栓塞をきたしにくいとされているため，欧米のように耳垢除去に関するガイドライン[5]はない．しかし，乾性耳垢であっても自浄作用の低下した高齢者では硬くうろこのようになった耳垢がはがれおちないまま蓄積し，難聴をきたすだけでなく，外耳道びらん，外耳道骨破壊までおこす重篤な事態に陥ることもある[3]．そのため，高齢者や補聴器を使用する人など耳垢塞栓のリスクが高い人[5]は，専門医による定期的な診察が必要であることを一般にも広く普及させることが求められる．また日本人の耳垢は，欧米人の湿性耳垢とは性質やたまり方が異なるため，欧米の報告がそのまま当てはまるわけではない．したがって今後は，我が国の耳垢ケアのあり方についてエビデンスを構築し，独自のガイドラインを作成することが肝要であろう．

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第54回日本老年医学会学術集会記録
〈シンポジウム6：認知症の地域連携〉

1. 三鷹市・武蔵野市の取り組み

長谷川　浩　　神﨑　恒一

Key words：認知症，地域連携，情報交換シート

（日老医誌　2013；50：194-196）

認知症患者の現状

現在，認知症高齢者は日本全国で240から300万人といわれている．杏林大学医学部付属病院のある東京都三鷹市は人口18万人，高齢化率19%であり，隣接する武蔵野市は人口14万人，高齢化率18%である．これらに日本全国での65歳以上の高齢者での認知症有病率12.4%という統計値を用いた場合，現在三鷹市で約4,000人，武蔵野市で約3,000人近い認知症高齢者がいると推計される．これに軽度認知障害を加え，しかも他の近隣の市，区を併せると，数万人の高齢者が認知症の精査もしくは治療の対象ということになる．これだけの数の認知症もしくはその疑いのある患者を地域でみていくためには，認知症専門医療機関のみでは到底不可能であり，地域の医療機関をはじめとする地域連携が必要である．

地域連携とその必要性

認知症患者を診るためには，専門医療機関とかかりつけ医との医療連携が必要であるほか，認知機能の低下自体が生活に障害をきたすという疾患の性質上，在宅で患者の生活を支える部門，すなわち，地域包括支援センターや在宅介護支援センターなど，介護，福祉，その他の行政部門が深くかかわる必要がある．しかしながら，在宅支援部門（ケアマネージャーなど）は認知症の疑いのある高齢者に対して，医療機関を受診させる具体的な手立てを有していないことが多い．一方，病院や診療所は介護保険の申請に始まり，ホームヘルプやデイサービスなど，地域資源の利用を進めるための知識や方法をもたないことが多く地域“医療”連携に終始することがある．

Community-based medico-social network for dementia: the experience of Mitaka-Musashino region
Hiroshi Hasegawa, Koichi Kozaki：杏林大学医学部高齢医学

地域包括支援センターに行くよう患者さんや家族に指示はするが，この指示だけでは患者さんや家族は具体的には動かないし，動けない．このように，それぞれの立場で知識不足，交流不足に基づく不便，困難を抱えている[1)~3)]．

三鷹武蔵野認知症連携

三鷹市と武蔵野市では両市の（1）地域包括支援センター，在宅介護支援センター，行政，(2) 両医師会，(3) 専門病院の連携体制を構築するため，三鷹・武蔵野認知症連携ワーキンググループを組織し（表1），平成20年より活動を開始した．当初より2カ月に1回，連携会議を開き，具体的な課題について検討を行ってきた．その中で，完成したのが情報交換シートである．

本連携は基本的に（I）在宅相談機関，(II) 相談医，(III) 専門医療機関の三者間の連携である（図1）．それぞれが上記（1）～（3）に対応するが，相談医はかかりつけ医を兼ねることも多く，初診であっても積極的に認知症診療にかかわることを了承した医師会所属の医師である．相談医は専門医療機関からの逆紹介を受け，定期的なフォローを行うこともある．

情報交換シートは三者間で双方向に行う形になっている．病診連携は④～⑥のシートを用いて行う．その際，シート⑤（専門医療機関から紹介医への報告書）には認知症の経過を診る上で必要な，日常生活自立度（基本的ADLと手段的ADL，JABC，I～IV，M），認知機能（MMSE，病期評価のためのFAST），うつ（GDS15），生活意欲（意欲の指標）など総合的機能評価のほか，周辺症状，画像としてMRIとSPECTの所見，診断名，治療方針（薬物療法と非薬物療法），患者，家族への説明内容などを記載するようになっている．逆方向のシート（紹介医→専門医；④と⑥）にはADL，周辺症状，治療内容と介護の状況などを記載する．これらのシート

表1　三鷹・武蔵野認知症連携ワーキンググループ

三鷹市	行政	三鷹市健康福祉部高齢者支援課5名
	地域包括支援センター	地域包括支援センター（主任ケアマネージャー）4名
	医師会	医師2名
	専門病院	杏林大学病院もの忘れセンター医師2名，認知症看護認定看護師2名，地域医療連携室3名 吉岡リハビリテーションクリニック 長谷川病院（精神科） 井之頭病院
武蔵野市	行政 地域包括支援センター	健康福祉部高齢者支援課，地域包括支援センター計6名
	在宅介護支援センター	在宅介護支援センター2名
	医師会	医師2名
	専門病院	武蔵野赤十字病院医師，ソーシャルワーカー

協力病院：慈雲堂病院（周辺症状対応病院）

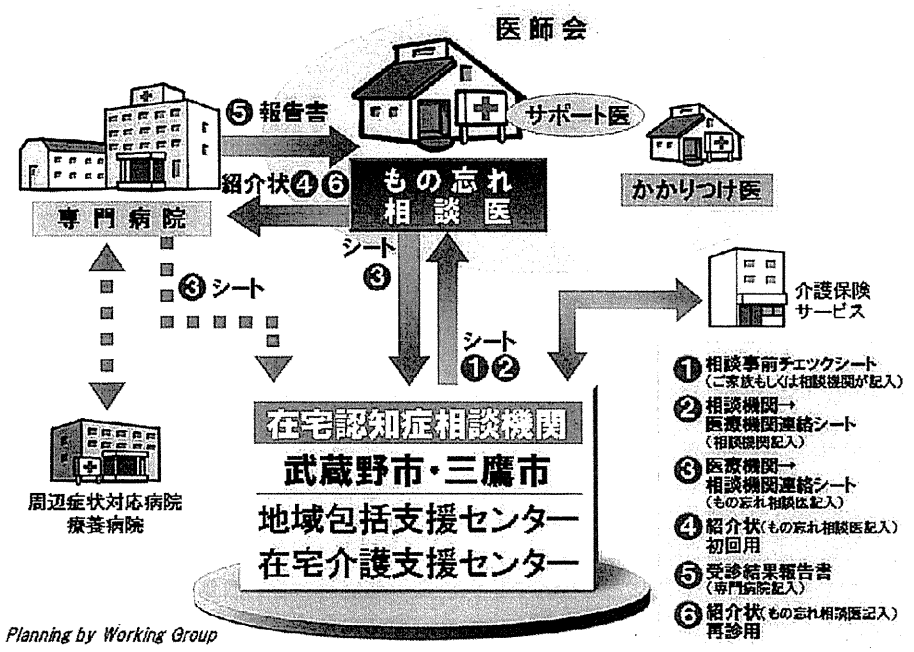

図1　三鷹武蔵野地区認知症連携イメージ

を用いて継続的に患者の評価を行う．また，以前は診断・治療に関する情報が，積極的に地域包括支援センター，在宅介護支援センターに伝えられることが少なかった．このため，本シートで特徴的かつ重要なのは③と考えられる．シート①②は，地域包括支援センターや在宅介護支援センターなどの在宅相談機関から，相談医や専門医に向けて，家族やケアマネージャー等が，認知症にかかわる日常生活上の問題点を記載するためのものであり，これを受けて相談医，専門医はシート③に，診断，治療方法を含めた受診結果，本人や家族への説明，導入すべきサービス内容，今後のフォローの予定などを在宅相談機関に返す．情報が一方向にならないよう，また，情報のやりとりが継続的に行えるよう工夫している．また，シートの利用の仕方を理解する手助けとして，“シートの目的と使い方”の説明書類を添付している．

三鷹武蔵野認知症連携の現状と課題

平成22年6月より上記シートの試験的運用を開始し

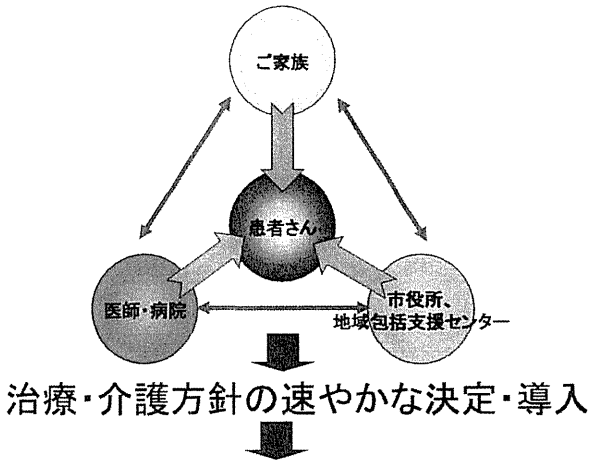

図2　認知症地域連携の理想的な形は…

ており，2カ月に1回開催されるワーキンググループ会議で，事例発表を行い，毎回成果を確認している．また，シートはより使いやすいものに改訂を行っている．運用しながら課題を見つけ，修正していくのが本ワーキンググループのやり方である．試用期間を経て平成23年11月より本格稼働を始めた．

情報交換シートの作成以外にワーキンググループでは，医師会での認知症研修会，相談医への参加表明の確認（上記），ケアマネ等を対象とした研修会，認知症サポーター養成，サポート医養成の援助などを行っている．認知症研修会では，認知症全般に関する勉強，シートの説明，事例検討などを行っている．有効な連携を築くためには，書面だけでなく顔の見える連携が重要と考えている．また，今後は市民向けの勉強会の開催も予定している．

なお，周辺症状が著しい患者への対応（入所，入院が必要な場合の受け入れ先の担保），在宅相談機関でも行える認知症早期診断バッテリーの開発と普及などが当面の課題である．

さらに認知症連携に求められるもの

認知症連携は，都市部と地方の違いなどで，各地域により求められる内容が異なる．このためその地域の必要な要素を強化し特化した方法が必要と考えられる．

また，当初患者さんや家族は，患者さんの一見おかしな言動や行動が認知症とは判断できず，どこに相談に行ってよいかわからなくなっていることが多い．大事なポイントとしては，患者さんや家族が最初に医師，市役所，地域包括支援センターのどこに相談しても，治療，介護の情報を入手することが出来，地域連携システムが回り始めることが肝要である（図2）．

また，認知症の患者さんが身体疾患（肺炎，心不全など）を発症した場合，どこで診るかが速やかに決定されることも重要であり，その患者さんが退院となった場合の行き先の決定も重要（直接自宅には戻れないケースもあるため）である．これらが速やかに決定されるためにも地域に密着した認知症医療・介護連携が重要と考えられる．

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Geriat. Med. 51(1)：31～34, 2013

特集　認知症治療の最前線―包括的ケアを踏まえた新しい治療戦略―

Seminar

1．非薬物療法と啓発活動
4）「もの忘れ教室」の実際とその効果

木村紗矢香　　神﨑　恒一

KEY WORD
●認知症
●非薬物療法
●家族教室
●周辺症状
●介護負担

SUMMARY

■周辺症状の増加は介護負担を悪化させる最大の要因とされており，患者が在宅での生活を継続するためには，周辺症状の緩和が肝要である．周辺症状の治療には，非薬物療法を優先することが基本とされており，杏林大学病院もの忘れセンターでは，患者と家族を支援することを目的として「もの忘れ教室」を実施している．「もの忘れ教室」は，疾患の正しい知識と対応の仕方や，社会資源に対する知識と活用の仕方を伝え，転倒予防，意欲向上，患者や家族の交流の場として機能しており，患者の周辺症状の悪化と介護負担の増大を予防する効果がある．

はじめに

認知症は根治が難しい疾患であるが，近年では薬剤を使用することによって，中核症状である認知機能の低下を遅らせることが可能となった．しかし認知症の治療には，患者がその人らしくいられるか，家族がどれだけ上手に患者を支えていけるか，といった在宅での生活をいかに継続させていくかという視点も重要である．

認知症患者を在宅で介護することは，家族に大きな負担を強いることがある．なかでも，周辺症状と介護負担には強い相関があり[1]，周辺症状の増加は介護負担を悪化させる最大の要因と考えられる．周辺症状には徘徊や暴力などの行動症状と，抑うつや不安などの精神症状がある．しかしながら，治療に用いられる薬物には認知機能や運動機能を障害する副作用があるため，非薬物療法を優先することが基本とされている[2]．非薬物療法には，レクリエーション療法や音楽療法，回想療法などの心理療法的アプローチから，介護者教育，環境への介入，通所サービス利用まで幅広く含まれ[3]，周辺症状に対する有効性が国内外で多数報告されている[4]．

杏林大学病院もの忘れセンターでは，患者が1日でも長く在宅での生活を続けることができるよう，患者と家族を支援することを目的として，「もの忘れ教室」を実施している．「もの忘れ教室」は疾患に対する正しい知識と対応の仕方や，社会資源に対する知識と活用の仕方を伝え，転倒予防，意欲向上，患者や家族の交流の場として機能している．

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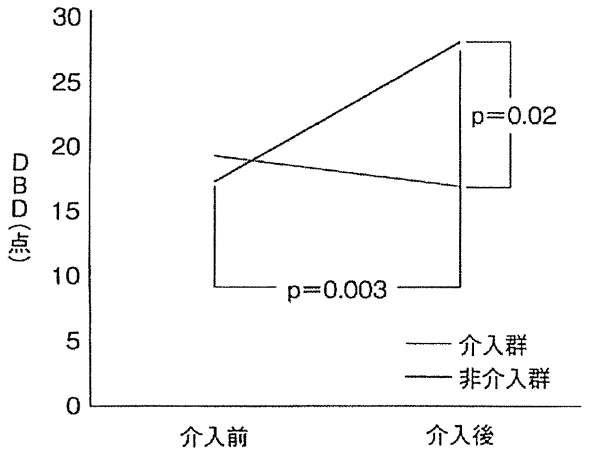

図1　周辺症状(DBD)の介入前後の比較

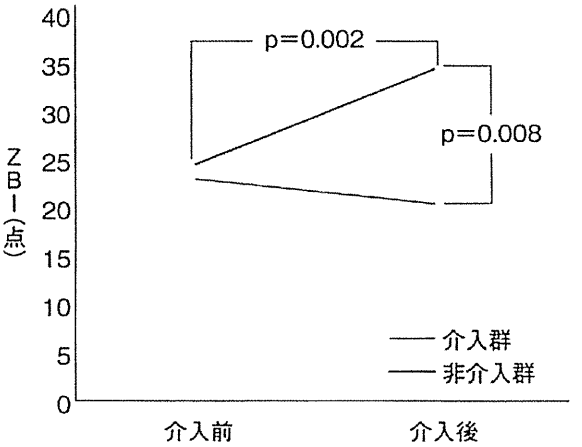

図2　介護負担(ZBI)の介入前後の比較

「もの忘れ教室」の内容と実施について

「もの忘れ教室」は，以下のテーマに基づき毎月6教室開催されている．

1）認知症とは何か
2）もの忘れの予防と治療
3）認知症との付き合い方
4）認知症の介護
5）運動療法
6）音楽療法

募集は，外来におけるポスターの掲示と，リーフレットの配布により行っているが，参加については患者と家族の意思に委ねている．また，どの教室にも患者と家族のどちらでも参加できるよう内容を工夫している．

「もの忘れ教室」の効用に関する調査研究

筆者らは以前，患者の周辺症状と家族の介護負担に着目し，「もの忘れ教室」の有効性を検討した．以下にその結果を報告する．

1．対象者と評価項目

もの忘れ教室に参加した患者22名(介入群)と，参加していない患者22名(非介入群)を対象として，「もの忘れ教室」介入前後に，周辺症状(Dementia Behavior Disturbance scale：DBD)と介護負担(Zarit Burden Interview：ZBI)に差がみられるかどうか，介入群と非介入群それぞれで群内比較した(対応ありt検定)．

2．結果(図1，2)

介入前後のDBDとZBIを群内比較した結果，介入群のDBD(前19.0±14.1，後16.8±12.3)とZBI(前22.8±21.5，後20.4±17.6)には有意な差はなかったが，どちらも低下する傾向が認められた．それに対して，非介入群のDBD(前16.8±8.6，後27.4±17.1)とZBI(24.8±13.6，後34.6±16.0)はどちらも有意に上昇していた．さらに，DBD，ZBIともに介入前には介入群と非介入群で有意な差はみられなかったが，介入後には有意な差がみられた．

「もの忘れ教室」に参加した患者の周辺症状と介護負担は低下する傾向が認められた．一方，参加しなかった患者の周辺症状と介護負担は有意に上昇していた．

「もの忘れ教室」の実際

以下，教室の実際の実施と，教室に参加した患者や家族の感想をまとめた．

1）「認知症とは何か」は，臨床心理士が担当し，認知症の症状や生活障害，周辺症状について説明をしている．患者の状態を正しく理解することで，家族は今後の見通しがもてるように

なるだけでなく，不安や混乱に陥ることなく介護を行うことができるようになる[5]．特に周辺症状については，対処法を適切に理解し実践するための介護者教育が重要であり[3]，周辺症状が起こる背景には記憶力障害や見当識障害，ADLの低下など様々な理由があることを理解してもらえるよう努めている．また，一方的に知識を伝えるだけでなく，認知症になったことによる患者の心理的葛藤や，家族の苦悩[6]にも十分に配慮することが大切である．

2）「もの忘れの予防と治療」は，医師が担当している．家族教育には，医師や看護師が医学的理解を促す「病気や障害についての教育」を取り入れることが有効である[5]．普段の診察時間には制限があり，医師がゆっくりと患者や家族に認知症について説明をするのは難しいことがある．また患者や家族も，診察室の中では，聞きたくても聞けなかった，意見を言えなかったということもある．そのため，医師と近い距離で対話できる貴重な機会となっているようである．

3）「認知症との付き合い方」は，認知症看護認定看護師が担当している．知識を身につけ病気や患者を理解しようと努めても，日々の介護からくるストレスや迷いは尽きない．また，孤独になりやすい家族にとって，仲間と気持ちを共有し，介護に関する様々な情報交換を行うことは大きな支えとなる[5]．ここでは，患者や家族が自分の気持ちや知っている情報を自由に話し，交流の機会となるような働きかけを行っている．家族からは，「自分たちの普段の対応が間違っていないことがわかった」，「これからも前向きに患者に向き合っていこうと思った」という意見が聞かれている．

4）「認知症の介護」は，社会福祉士が担当し，介護保険の仕組みや申請の仕方を伝えている．当センターの初診患者の約54%が介護保険未申請である．介護保険の存在を知らない家族や，利用申請の手続きにストレスを感じる家族などその理由は様々である．また，なかには最後まで自分で介護したいと考える家族もいる．しかし，在宅で生活を続けるためには，介護者という役割から解放されて休むために介護サービスを利用することが必要なこともある．介護保険を利用するまでに至る家族の気持ちにも配慮しながら，上手に介護保険を活用できるよう家族を支援していくことが大切である．

5）「運動療法」は，気功と太極拳の専門家が担当している．太極拳は，高齢者の身体機能を向上させるだけでなく，転倒予防の効果もある[7]．本格的な運動だけでなく，車椅子に乗ったままでもできる運動や，手をすり合わせるといった簡単な運動も取り入れ，参加者の状態に合わせた工夫をしている．参加した患者や家族からは，「気分転換になった」「楽しかった」という声が聞かれている．また，家族同伴で参加してもらうことによって，1人では運動を続けることが難しい患者が在宅でも運動を継続できるという効果もあるようだ．

6）「音楽療法」は，音楽療法士が担当している．音楽療法は，単に歌を歌ったり音楽を聴いたりすることとは違い，音楽療法士が個々のニーズに合わせて音楽を提供し，成果を分析しながら行う支援の方法である[8]．当院の音楽療法は特に女性に人気がある．家族同伴で参加できるため，音楽を楽しむだけでなく，患者や家族がお互いに楽しんでいる様子をみることも喜びとなり，患者や家族にとってよい交流の場となっている．

まとめ

以上の取り組みから，「もの忘れ教室」は包括的に患者の周辺症状の悪化を予防し，それが結果的に介護負担の軽減することにつながっていると考えられる．

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ORIGINAL ARTICLE: EPIDEMIOLOGY, CLINICAL PRACTICE AND HEALTH

Interview- and questionnaire-based surveys on elderly patients' wishes about artificial nutrition and hydration during end-of-life care

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Aim: To promote advance directives, it is crucial to understand how many older persons have wishes related to end-of-life care. Additionally, it is important to understand how cognitive function or mood affect these wishes.

Methods: For the interview-based survey, 99 inpatients aged 75 years or older were enrolled after excluding patients with a Mini-Mental State Examination score of 20 or less. For the questionnaire-based survey, 99 outpatients aged 75 years or older without dementia were enrolled. Both surveys comprised the same items on older patients' wishes related to artificial nutrition and hydration (ANH) during end-of-life care.

Results: Of the total enrolled patients, 76.8% participated in the interviews. Of these, 50.0% were against ANH during their end-of-life care, including the patients who were definitely against ANH (26.3%). In contrast, just 5.3% wished to receive ANH. In the questionnaire survey, 65.6% of the respondents were against ANH, and 4.9% wished to receive ANH. Aging and Mini-Mental State Examination scores of less than 24 were significantly associated with a higher tendency to decline from participating in the interview. However, the distribution of the interview answers was not associated with age, Mini-Mental State Examination or Geriatric Depression Scale scores. Of the interviewed patients, 84.2% agreed to their responses being preserved in their medical records.

Conclusions: Although the majority of the elderly patients were against ANH during end-of-life care, many patients did not have definite wishes in Japan. The percentage of those who were against ANH was not associated with cognitive function or depressive state. **Geriatr Gerontol Int ••; ••: ••–••.**

Keywords: advance care planning, advance directive, artificial nutrition and hydration, end-of-life care, interview.

Introduction

The aged society makes it increasingly important to understand how to care for the elderly at the end stage of their lives.[1,2] One area of concern is that the majority of elderly patients with advanced dementia have trouble with nutrition as a result of loss of appetite or dysphagia.[3] Specifically, they frequently develop a fever and are finally diagnosed as unable to receive enough oral nutrition. In many cases in Japan, artificial nutrition and hydration (ANH) through gastrostomy, nasal tube or central venous catheter is initiated,[4,5] although the beneficial effects of any of these methods have not been reported in previous investigations.[6–8]

Contemporarily, many medical societies and doctors have shown great concern about the use of ANH in advanced dementia.[7] However, the caregivers and primary healthcare professionals of patients with dementia are challenged to forgo ANH, because this decision can directly relate to the patients' lives.[9,10]

Although advance directives can be very useful for caregivers and healthcare team members in deciding on the best patient end-of-life treatment,[8,11,12] they are not prevalent enough in Japan.[13,14] Various factors prevent elderly patients from making advance directives.[15] For

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Note: Supplementary information is available on the Geriatrics & Gerontology International website.

instance, elderly patients might not want to talk with family members, especially children, about their death. Furthermore, elderly patients might not have strong wishes about their future care.

To understand the usefulness of advance directives, we first need to know how many elderly patients have wishes about their own end-of-life care. However, most previous studies pertaining to thoughts about ANH during this stage have focused on younger people, such as healthcare professionals and community-dwelling adults.[14,16–18] We investigated elderly patients' own wishes regarding ANH for the time when they reached the end-of-life stage in the future. To reflect wishes related to advance directives, participants were informed that, if they consented, answers would be preserved in their medical records. In addition, we carried out a questionnaire-based survey to evaluate how interview-based methods affect answer distributions.

Methods

Study design

We carried out two styles of surveys on the wishes regarding ANH during end-of-life care; that is, interview- and questionnaire-based surveys. In the interview-based survey, a doctor interviewed elderly inpatients in a private room without any consultation with family members. The interview was carried out after the completion of scheduled examinations. Patients' consent was confirmed twice, once before and once after the interview. The latter one included consent about the preservation of answers in their medical records.

The questionnaire-based survey was carried out by providing elderly outpatients with a questionnaire with the same items as the interview-based survey. The completed questionnaires were mailed or returned to the researchers without identification of the respondent. Returning the survey was regarded as consent to survey participation. In the questionnaire-based survey, responses were not retained in medical records unless patients made this request.

The study protocol was approved by the institutional review board of the Graduate School of Medicine, University of Tokyo.

Participants

The participants of the interview-based survey were recruited consecutively from the population of inpatients aged 75 years or older admitted for examination at the Faculty of Geriatric Medicine, The University of Tokyo Hospital, Tokyo, Japan. Data collection occurred from September 2012 to June 2014. Patients admitted for emergencies for acute diseases were excluded. We also excluded patients whose prognosis was estimated to be less than 2 years for uncured malignant tumors and interstitial pneumonia. The Mini-Mental State Examination (MMSE), Geriatric Depression Scale (GDS), Barthel Index and Lawton Instrumental Activities of Daily Living (IADL) Index were administered to all potential participants, and those with a score of 20 or less on the MMSE were excluded. In addition, patients whose medical documents had shown some unreasonable complaints or anxieties about medical examination or intervention were excluded, as determined by the primary doctors or interviewers. Finally, 99 patients were requested to participate in the interview.

The participants of the questionnaire-based survey were recruited consecutively from the outpatients aged 75 years or older at the Faculty of Geriatric Medicine, The University of Tokyo Hospital from March 2014 to June 2014. The patients who had already been recruited to the interview survey were not enrolled in the questionnaire survey. Although the MMSE was not carried out on all outpatients, primary doctors judged patients' levels of cognitive function, and the patients with dementia were excluded. The other exclusion criteria were the same as those of the interview survey. Finally, the questionnaire was distributed to 99 patients.

Interview and questionnaire contents

The same items were used for both interview- and questionnaire-based surveys (Supplementary Appendix SI). In the interview survey, an interviewer read the explanations and questions with minor modifications for the oral approach and participant responses.

First, the background of the survey was explained. Subsequently, only in the interview survey, we informed participants that the answers would be preserved in their medical records, if they consented.

After explaining the effectiveness and complications of feeding through gastrostomy, nasal tube and intravenous hyperalimentation to participants (Supplementary Appendix SII), the questions were initiated as follows (Supplementary Appendix SI).

Assuming that the participant was in a state preventing his/her ability to walk, maintain conversation and eat enough, three questions were asked.

Question 1, "If necessary to live, would you like to start using a gastrostomy tube or nasal tube?" The response options were: answer 1, "I definitely want to start"; answer 2, "If anything, I want to start"; answer 3, "I don't know"; answer 4, "If anything, I do not want to start"; or answer 5, "I definitely do not want to start."

Question 2, "If necessary to live, would you like to start intravenous hyperalimentation?" The possible response options were the same as question 1.

Question 3, "Do you believe it is acceptable to die as the result of undernutrition?" The response options

were: answer 1, "Definitely unacceptable"; answer 2, "If anything, I would consider it unacceptable"; answer 3, "I don't know"; answer 4, "If anything, I would consider it acceptable"; or answer 5, "Definitely, acceptable."

Additionally, we asked participants if they had discussed ANH during end-of-life care with others.

Patient grouping based on participant responses to each question

Hereafter, patients who responded that they did not want to start tube feeding or intravenous hyperalimentation, and that it is acceptable to die as the result of undernutrition (i.e. chose answers 4 or 5 for all three questions) were referred to as the "No ANH" group. Among the "No ANH" group, some responded that they definitely did not want to start tube feeding or intravenous hyperalimentation, and that it is definitely acceptable to die as the result of undernutrition (i.e. chose answer 5 for all three questions). These patients were referred to as the "Definitely, No ANH" group. Patients who responded that they wanted to start tube feeding and intravenous hyperalimentation, and that it is not acceptable to die as the result of undernutrition were referred to as the "Pro ANH" group (i.e. chose answers 1 or 2 for all three questions). The other patients were referred to as the "Undecided" group; this group comprised the patients who chose answer 3 (I don't know) for some of questions 1, 2 and 3, and the patients who had inconsistent answers (i.e. chose answers 1 or 2 for some questions and answers 4 or 5 for the other questions).

Statistical analysis

Because all background data significantly deviated from normality as shown by the Shapiro–Wilk test, the Mann–Whitney *U*-test was used to compare interviewed patients and those that did not participate in the interview. The χ^2-test or Fisher's exact test was used to compare categorical variables, such as sex, the number of patients with each existing disease and answers to the questions about ANH. To determine the factors that influenced interview consent, the odds ratios (OR) and 95% confidence intervals (CI) were calculated using multiple logistic regression analysis. All statistical analyses were carried out using the SPSS software program (version 19.0; SPSS, Chicago, IL, USA). Statistical significance was defined as P-values < 0.05.

Results

Answer distribution in the interview-based and questionnaire-based surveys

In the interview-based survey, 126 patients were consecutively recruited as stable patients with MMSE scores of 21 or higher. A total of 18 patients were excluded because their medical records showed some unreasonable complaints or anxieties about medical examination or intervention. Nine patients were not interviewed because they had no time available. Among the remaining 99 patients who were requested to participate in the interview, 76 patients (76.8%) agreed to participate in the interview. Characteristics of these patients are shown in Table 1. The distributions of their responses to questions 1, 2 and 3 are shown in Table 2.

In the questionnaire-based survey, 104 patients were recruited as patients without dementia. Five patients were excluded because their medical records showed some unreasonable complaints or anxieties. The characteristics of the 99 enrolled patients are shown in Table 1. Of these 99 patients, 61 (61.6%) responded to the questionnaires. The distributions of their responses to questions 1, 2 and 3 are shown in Table 2.

The ratio of the patients who selected the option "I don't know" was higher for all the questions in the interview survey than it was in the questionnaire survey ($P = 0.07$, $P = 0.001$, $P < 0.001$, on question 1, 2 and 3, respectively). As for the other answers, the number of the patients against ANH (answers 4 and 5) per the number of the positive patients about ANH (answers 1 and 2) were not significantly different among questions 1, 2 and 3, or between the interview survey and questionnaire survey (Table 2).

To compare tube feeding and intravenous hyperalimentation, we also evaluated the answer combinations for questions 1 and 2. The number of inconsistent answers for questions 1 and 2 (i.e. chose answers 1 or 2 for one question, and answers 4 or 5 for the other question) was only one for both the interview survey and the questionnaire survey (Supplementary Table S1).

The patient grouping in the interview survey showed that the "No ANH" group comprised 38 patients (50.0% of the interviewed patients), including 20 patients from the "Definitely, No ANH" group (26.3% of the interviewed patients). The "Pro ANH" group had just four patients (5.3% of the interviewed patients). The "Undecided" group comprised the remaining 44.7% of the interviewed patients. The questionnaire survey showed that the "No ANH" group comprised 40 patients (65.6% of the patients who responded), including 22 patients from the "Definitely, No ANH" group (36.1% of the patients who responded). The "Pro ANH" group had just three patients (4.9% of the patients who responded; Supplementary Table S1).

Factors influencing interview consent and ANH answers

First, we evaluated the factors that influenced interview consent. We found that age, percentage of MMSE

Table 1 Baseline characteristics of the enrolled patients

	Interview Total $n = 99$	Interviewed $n = 76$	Non-interviewed $n = 23$	*P*-value	Questionnaire Total $n = 99$
Age (years)	81.5 (5.0)	80.9 (4.5)	83.3 (6.1)	0.100	80.6 (4.8)
Males/females	47/52	38/38	9/14	0.360	60/39
MMSE score	26.7 (2.5)	26.9 (2.4)	25.8 (2.5)	0.066	
MMSE score ≤23	11.1%	6.6%	26.1%	0.018	
GDS15	5.0 (3.4) ($n = 97$)	4.7 (3.1) ($n = 74$)	5.9 (4.1) ($n = 23$)	0.252	
GDS15 score ≥10	11.3%	8.1%	21.7%	0.082	
Barthel Index	94.3 (11.7) ($n = 96$)	94.5 (12.6) ($n = 74$)	93.9 (8.2) ($n = 22$)	0.223	
Lawton IADL (males)	4.4 (1.0) ($n = 46$)	4.6 (0.9) ($n = 37$)	3.7 (1.2) ($n = 9$)	0.036	
Lawton IADL (females)	6.4 (1.8) ($n = 50$)	6.4 (1.7) ($n = 37$)	6.5 (2.2) ($n = 13$)	0.729	
Diseases					
Hypertension (%)	68.7%	68.4%	69.6%	0.917	57.6%
Diabetes (%)	21.2%	26.3%	4.3%	0.017	12.1%
Sleep apnea syndrome (%)	23.2%	26.3%	13.0%	0.187	39.4%
Cerebrovascular disease (%)	6.1%	6.6%	4.3%	0.574	3.0%
Ischemic heart disease (%)	5.1%	3.9%	8.7%	0.329	9.1%
Chronic heart failure (%)	7.1%	6.6%	8.7%	0.515	6.1%
Parkinson (%)	4.0%	3.9%	4.3%	0.659	0.0%
Chronic pain (%)	13.1%	11.8%	17.4%	0.352	9.1%
Osteoporosis (%)	28.3%	23.7%	43.5%	0.065	17.2%
Hyperlipidemia (%)	36.4%	36.8%	34.8%	0.857	33.3%
Insomnia (%)	22.2%	23.7%	17.4%	0.525	18.2%
COPD, bronchial asthma (%)	10.1%	9.2%	13.0%	0.422	15.2%

The values represent the means (SD) where applicable. The comorbidities indicate the percentage of the patients who were treated for each disease. *P*-value was obtained by comparison between the interviewed and non-interviewed patients. COPD, chronic obstructive pulmonary disease; IADL, instrumental activities of daily living; GDS15, Geriatric Depression Scale; MMSE, Mini-Mental State Examination.

Table 2 Answer distribution in the interview-based survey and questionnaire-based survey

		Answer 1 *n* (%)	2 *n* (%)	3 *n* (%)	4 *n* (%)	5 *n* (%)	(Answers 4 and 5) per (answers 1 and 2)	*P*-value *vs* interview	*P*-value *vs* Q1
Interview ($n = 76$)	Q1	3 (3.9%)	9 (11.8%)	19 (25.0%)	18 (23.7%)	27 (35.5%)	3.75	–	–
	Q2	3 (3.9%)	6 (7.9%)	25 (32.9%)	19 (25.0%)	23 (30.3%)	4.67	–	0.655
	Q3	5 (6.6%)	2 (2.6%)	23 (30.3%)	19 (25.0%)	27 (35.5%)	6.57	–	0.277
Questionnaire ($n = 61$)	Q1	3 (4.9%)	1 (1.6%)	10 (16.4%)	18 (29.5%)	29 (47.5%)	11.75	0.054	–
	Q2	3 (4.9%)	7 (11.5%)	8 (13.1%)	18 (29.5%)	25 (41.0%)	4.30	0.872	0.100
	Q3	4 (6.6%)	4 (6.6%)	5 (8.2%)	17 (27.9%)	31 (50.8%)	6.00	0.870	0.292

Question 1 was "If it is necessary to live, would you like to start using a gastrostomy tube or a nasal tube?" Answer 1, "I definitely want to start"; answer 2, "If anything, I want to start"; answer 3, "I don't know"; answer 4, "If anything, I do not want to start"; and answer 5, "I definitely do not want to start." Question 2 was "If it is necessary to live, would you like to start intravenous hyperalimentation?" The five possible response options were the same as Question 1. Question 3 was "Do you believe it is acceptable to die as the result of undernutrition?" The five possible answers were: answer 1, "Definitely unacceptable"; answer 2, "If anything, I would consider it unacceptable";answer 3, "I don't know"; answer 4, "If anything, I would consider it acceptable"; and answer 5, "Definitely acceptable." (Answers 4 and 5) / (answers 1 and 2) was calculated by the number of the patients with answers 4 or 5 divided by the number of the patients with answers 1 or 2. *P*-values were obtained by comparing (answers 4 and 5) / (Answers 1 and 2) using the χ^2-test.

Table 3 Associations between the background factors and the answers about artificial nutrition and hydration

			Pro ANH	*P*-value	No ANH	*P*-value	Definitely, No ANH	*P*-value
			n (%)		*n* (%)		*n* (%)	
Sex	Male	*n* = 38	3 (7.9%)	0.307	15 (39.5%)	0.066	9 (23.7%)	0.602
	Female	*n* = 38	1 (2.6%)		23 (60.5%)		11 (28.9%)	
Age	≥80	*n* = 42	2 (4.8%)	0.609	23 (54.8%)	0.356	11 (26.2%)	0.978
	<80	*n* = 34	2 (5.9%)		15 (44.1%)		9 (26.5%)	
MMSE (cut-off 26/27)	≥27	*n* = 43	3 (7.0%)	0.414	22 (51.2%)	0.817	12 (27.9%)	0.719
	21–26	*n* = 33	1 (3.0%)		16 (48.5%)		8 (24.2%)	
MMSE (cut-off 23/24)	≥24	*n* = 71	4 (5.6%)	0.757	36 (50.7%)	0.500	19 (26.8%)	0.604
	21–23	*n* = 5	0 (0.0%)		2 (40.0%)		1 (20.0%)	
GDS (cut-off 9/10)	≥10	*n* = 6	0 (0.0%)	0.708	4 (66.7%)	0.446	2 (33.3%)	0.487
	≤9	*n* = 68	4 (5.9%)		33 (48.5%)		17 (25.0%)	
GDS (cut-off 4/5)	≥5	*n* = 36	3 (8.3%)	0.287	18 (50.0%)	1.000	10 (27.8%)	0.687
	≤4	*n* = 38	1 (2.6%)		19 (50.0%)		9 (23.7%)	
Barthel Index	100	*n* = 54	3 (5.6%)	0.706	25 (46.3%)	0.295	14 (25.9%)	0.935
	<100	*n* = 20	1 (5.0%)		12 (60.0%)		5 (25.0%)	
Lawton Index (male)	5	*n* = 27	2 (7.4%)	0.624	11 (40.7%)	0.635	7 (25.9%)	0.537
	≤4	*n* = 10	1 (10.0%)		4 (40.0%)		2 (20.0%)	
Lawton Index (female)	8	*n* = 15	1 (6.7%)	0.405	7 (46.7%)	0.191	3 (20.0%)	0.342
	≤7	*n* = 22	0 (0.0%)		15 (68.2%)		7 (31.8%)	

The χ^2-test or Fisher's exact test was carried out to compare the ratio of the answers regarding artificial nutrition and hydration (ANH) between the two groups. The *P*-values are shown. GDS, Geriatric Depression Scale; MMSE, Mini-Mental State Examination.

scores of less than 24, percentage of GDS scores of 10 or more, and comorbidities of diabetes mellitus and osteoporosis differed between the interviewed and non-interviewed patients (Table 1). Subsequently, we carried out a multiple logistic regression analysis (forward selection method) using these factors as independent variables. As Lawton IADL scores showed collinearity with MMSE scores of 23 or less among males, we did not utilize the Lawton IADL score as an independent variable. Only MMSE scores of 23 or less and age showed a significant association with interview consent (OR 5.097, 95% CI 1.337–19.434; $P = 0.017$, and OR 1.105, 95% CI 1.005–1.214; $P = 0.038$, in order).

We also evaluated the association between the distribution of answers about ANH and various background factors (i.e. sex, age, MMSE, GDS, Barthel Index and Lawton IADL index). No factors significantly influenced the percentage of "Pro ANH," "No ANH" or "Definitely, No ANH" answers in the total obtained answers (Table 3). No background diseases showed any significant associations with the answers about ANH. In terms of MMSE scores, we applied cut-off points 26/27 and 23/24, because just five patients with MMSE scores of 23 or less could be interviewed. Likewise, cut-off points 4/5 and 9/10 for GDS scores were used, because just six patients with GDS scores of 10 or higher could be interviewed.

Percentage of the answers preserved in medical records

We found that 64 patients (84.2% of the interviewed patients) from the interview survey agreed to their responses being preserved in their medical records. Specifically, all of the four "Pro ANH" patients, and 35 of the 38 "No ANH" patients agreed to have their answers preserved in their medical records (92.9%), showing a significant difference from the patients who selected the option "I don't know" in some questions (71.0%; $P = 0.013$).

Of importance, we found that just 21 of the 76 interviewed patients (27.6%) had discussed ANH during end-of-life care with others. Furthermore, just 11 of the 20 "Definitely, No ANH" patients (55%) had discussed this topic with others. Likewise, just 18 of the 37 "No ANH" patients (48.6%) had previously discussed this topic.

Discussion

In the present study, we showed the percentage of elderly patients that were against ANH during end-of-life care. In our interview survey, 26.3% of the interviewed patients were definitely against ANH during end-of-life care. We speculate that these patients are already

prepared to make an advance directive if it is introduced. Consistent with previous surveys, the number of "Pro ANH" patients was very low,[9,17] and showed a serious gap from the actual prevalence of ANH in Japan.[5]

Importantly, our findings also showed that many elderly patients did not have clear wishes about their end-of-life care. Nearly half of the interviewed patients were included in the "Undecided" group. This high percentage in the "Undecided" group was partially explained by the simplified grouping of the three questions, namely, the patients who responded "I don't know" to one of the three questions were all included in the "Undecided" group. However, only approximately 30% of the patients in the interview survey responded "I don't know" to any of the questions, which is not a negligible number. Furthermore, only approximately 40% of the patients selected definite answers (i.e. answers 1 or 5) for any of the questions in the interview survey. It is important to encourage elderly patients to think about their own future end-of-life care, and at the same time, to create a method of a comprehensive decision-making process to be used for cases in which the wishes are not clearly expressed.

The comparison of the two survey methods suggested that the questionnaire-based survey obtained responses only from participants who had a clear idea of what they wanted, because the response rate for "I don't know" was significantly lower in the questionnaire-based survey than in the interview-based survey. The number of patients who wanted to start tube feeding was lower in the questionnaire-based survey than in the interview-based survey, although the difference was not statistically significant. A negative image of gastrostomy might have affected participants' responses in the questionnaire-based survey, as they did not have interviewers' explanations. The other answer distributions were almost similar between the two surveys.

Our findings also suggested that cognitive decline prevents patients from participating in discussion of these issues, although their reasons for rejection were not well determined. This result is reasonable, because dementia frequently involves passive behavior.[19] Although cognitive dysfunction does not necessarily imply an impossibility of self-determination, it would require more effort to ascertain the wishes of patients with dementia.[20]

At the same time, we could not find any factors that significantly influenced thoughts about ANH. This finding is rather important, suggesting that declining cognitive function or ADL, fluctuation of depressed mood, or old age would not substantially affect thoughts about ANH. This finding is consistent with a recent systematic review of longitudinal studies about end-of-life preferences.[21]

Many of the patients never discussed these issues with others. Thus, our investigation was the first to ascertain and preserve these wishes utilizing only simple interviews (approximately 20 min per patient). Importantly, most of the patients who expressed some wishes agreed to have their answers preserved in their medical records. Although real decision-making would still be complicated and difficult, these documents could have some effect on future end-of-life care decisions, even in the cases without strong wishes.[22] We speculate that our surveys showed a potentially novel method of advance care planning.

There are some limitations associated with the present study. First, the participants of our investigation were recruited from a single institution. In addition, a substantial number of inpatients had some uncontrolled anxiety or irritability, and were excluded from the survey. However, the similarity in the findings from the interview survey on inpatients and the questionnaire survey on outpatients would support the generalizability of our findings. Second, to clarify the association between dementia or depression and ANH preference, more subjects with MMSE scores of less than 24 or with GDS scores of more than 9 would be required. However, the cut-off point of less than 27 for the MMSE can be also utilized for screening mild cognitive impairment,[23] and the cut-off point of 5 or more on the GDS is frequently utilized for screening depressive state.[24] Thus, our findings support the notion that the presence of mild cognitive impairment or depressive state does not affect ANH preference. Third, we cannot know precisely, even through interviews, what the patients assumed from our explanations. This point would be most difficult to address in advance care planning for elderly patients.

In conclusion, our investigations showed the distributions of elderly patients' wishes regarding ANH during end-of-life care, when these are preserved in medical records, simulating an advance directive. Although the majority of the patients were against ANH, many elderly patients did not express definite wishes on this issue in Japan. In addition, our findings suggested that patients with cognitive impairment tended to avoid discussing these issues. However, we also found that the percentage of the wishes against ANH was not associated with the presence of mild cognitive impairment or depressive state.

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Disclosure statement

No potential conflicts of interest were disclosed.

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Supporting information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Table S1 Answer combinations for the interview- and questionnaire-based surveys.
Appendix SI English translation of the questionnaire.
Appendix SII Explanatory document.

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Protective effects of NMDA receptor antagonist, memantine, against senescence of PC12 cells: A possible role of nNOS and combined effects with donepezil

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ABSTRACT

Alzheimer disease (AD) is a neurodegenerative disorder characterized by cognitive dysfunction. The pathology of AD is mainly related to amyloid ß (Aß)-peptides, but glutamate-mediated toxicity is also one of the main processes of memory impairment in AD. Glutamate is the main excitatory neurotransmitter in the central nervous system (CNS) and is particularly involved in synaptic plasticity, memory, and learning. Memantine is a low-affinity voltage-dependent noncompetitive antagonist at glutamatergic NMDA receptors. Here, we investigated whether memantine protects against glutamate-induced senescence. In PC12 cells, treatment with glutamate induced senescent phenotypes as judged by the cell appearance and senescence-associated ß-galactosidase (SA-ßgal) in parallel with decreased SIRT1 and increased p53 expression. However, treatment with memantine decreased glutamate-induced senescent PC12 cells and reversed the changes in SIRT1 and p53 expression. Glutamate is known to stimulate the production of NO and O_2^- and has the capacity to generate $ONOO^-$ in the CNS. Therefore, we investigated whether glutamate activates nNOS and memantine reverses it. Treatment with glutamate increased nNOS expression, activity, and production of NO, whereas memantine blocked them. Next, the in vivo effects of memantine on cognitive function in senescence-accelerated mouse prone 8 (SAMP8), as a model of AD, were investigated. In the Morris water maze test, SAMP8 showed a marked decline in performance, but memantine administration improved it. Moreover, neuronal senescence and the level of oxidative stress in the hippocampus were decreased by memantine. Finally, the effects of combination treatment with memantine and donepezil, a cholinesterase inhibitor, were investigated. We observed additive effects of memantine and donepezil on the senescent phenotype of PC12 cells and the hippocampus of SAMP8. These results indicate that inhibition of the NMDA receptor by memantine leads to a decrease in nNOS activity and results in a reduction of glutamate-induced senescence. Thus, our present study suggests a critical role of memantine in the prevention of neuronal aging, and supports that donepezil has a combined effect with memantine.

1. Introduction

Alzheimer disease (AD) is a progressive, neurodegenerative disease characterized by a gradual decline in cognitive function. The etiology of AD is mainly attributable to Aß peptides or tau aggregates, and evidence also exists for both cholinergic and glutamatergic involvement in AD (Ingram et al., 1996). Acetylcholine (Ach), a neurotransmitter essential for processing memory and learning, is decreased in both concentration and function in patients with AD. Similarly, glutamate is the main excitatory neurotransmitter in the CNS and plays a pivotal role in learning and memory. Unlike Ach, glutamate leads to over-activation of N-methyl-D-aspartate (NMDA) receptors and results in neuronal damage. Since over-activation of NMDA receptors increases the amount of intracellular Ca^{2+}, glutamate activates neuronal nitric oxide synthase (nNOS), which produces nitric oxide (NO) and leads to production of reactive oxygen species (ROS; $ONOO^-$), which may trigger neuronal damage (Doucet et al., 2015).

Oxidative stress is known to be closely related to cellular senescence and age-related diseases associated with AD (Tacutu et al., 2011). An increase in oxidative stress has been suggested to be one of the earliest pathological changes in the brain in cognitive impairment due to AD (Mattson, 2004). Cellular senescence of neuronal cells, as well as of

Abbreviations: Aß, amyloid ß; Ach, acetylcholine; AD, Alzheimer disease; CNS, central nervous system; DAF-2, diaminofluorescein-2; DAPI, 4′, 6-diamidino-2-phenylindole; e, i, nNOS, endothelial, inducible, neuronal nitric oxide synthase; HUVEC, human umbilical vein endothelial cells; L-VNIO, N^5-(1-amino-3-butenyl)-L-ornithine; MTS, 3-(4, 5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulphophenyl)-2H-tetrazolium; NMDA, N-methyl-D-aspartate; PBS, phosphate-buffered saline; SAMP8, senescence-accelerated mouse prone 8; SAMR1, senescence-accelerated mice resistant 1; SA-ßgal, senescence-associated ß-galactosidase; ROS, reactive oxygen species.

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peripheral cells, has been described in AD and causes cellular dysfunction (Naylor et al., 2013).

Memantine (1-amino-3, 5-dimethyladamantane hydrochloride), a noncompetitive NMDA receptor antagonist, was approved about ten years ago for the treatment of moderately severe to severe AD (2002 EU, 2003 USA, since 2011 in Japan). Its effectiveness for cognition has been shown in randomized placebo-controlled trials in patients with AD (Areosa et al., 2005). Since memantine is able to prevent pathogenic Ca^{2+} influx caused by stimulation with glutamate, we considered that the effects of memantine may reduce oxidative damage to neuronal cells and inhibit cellular senescence. In the present study, we showed that glutamate induces senescence of PC12 cells and memantine inhibits nNOS activity, reduces oxidative damage and results in protection against glutamate-induced senescence.

Furthermore, donepezil, a cholinesterase inhibitor, has been used widely in combination with memantine for the treatment of AD patients. Thus, we also examined the combined effects of memantine and donepezil.

2. Materials and methods

2.1. Materials

Glutamate, MK-801, donepezil, and N^{ω}-propyl-L-arginine were purchased from Sigma (St. Louis, MO, USA). Memantine was provided by Daiichi Sankyo Company, Limited (Tokyo, Japan).

2.2. Cells

PC12 cells were purchased from ATCC (Manassas, VA, USA). They were cultured and treated with 2.5S nerve growth factor (NGF, 50 ng/ml, Alomone Labs Ltd., Jerusalem, Israel) to induce differentiation into neuronal cells (Ogawa et al., 1984). Human umbilical vein endothelial cells (HUVEC) were purchased from Cambrex (Walkersville, MD, USA).

2.3. NOS activation assay

NOS activity was determined using an NOS assay kit (Calbiochem) according to the manufacturer's instructions. NO production was observed using fluorescent dye diaminofluorescein-2 (DAF-2) (Daiichi Pure Chemicals Co., Ltd., Tokyo, Japan). Briefly, PC12 cells were loaded with DAF-2 (5 μM for 30 min at 37 °C) and then washed three times with phosphate-buffered saline (PBS). Green fluorescence intensity (DAF-2) was visualized with 4′, 6-diamidino-2-phenylindole (DAPI) (blue) (Dojindo Molecular Technologies, Inc., Tokyo, Japan) for nuclear staining. Fluorescent images were analyzed using a fluorescence microscope (BZ-9000, Keyence, Osaka, Japan).

2.4. Animal experiments

Animal experiments were carried out in accordance with the National Institute of Health Guide for the Care and Use of Laboratory Animals (NIH Publications No. 80-23) revised 1996. Senescence-accelerated mice prone (SAMP) 8 and control senescence-accelerated mice resistant (SAMR) 1 male mice were all housed and maintained in a room at 22 ± 2 °C with automatic light cycles (12 h light/dark) and relative humidity of 40–60%. Mice were purchased from Japan SLC, Inc. (Shizuoka, Japan). Food and tap water were provided ad libitum throughout the study. In the water maze test of this study, groups of male SAMR1 (N = 5) and SAMP8 (N = 5) were first tested. Male mice of 12 weeks of age were treated daily for 3 weeks with memantine (10, 20 mg/kg), MK-801 (10 mg/kg), or donepezil (0.3 mg/kg) by subcutaneous injection (s.c) in the neck before the water maze test. Mice were anesthetized, and killed by cervical dislocation. The brain was removed for histological examination, after systemic perfusion with PBS.

2.5. Morris water maze test

The procedure of the Morris water maze test was described previously (Cao et al., 2007). Briefly, SAMR1 (N = 5) and SAMP8 mice (N = 5) were trained to find a visible platform with three trials on the first day, and then tested to find the hidden platform for 10 consecutive days. In each trial, the mice were allowed to swim until they found the hidden platform, or until 2 min had passed, and the mouse was then gently guided to the platform. On the test days, the platform was hidden 1 cm beneath the water. Probe tests were performed on the 10th day. The maze was conceptually divided into I, II, III, and IV, four equal quadrants by four poles along the perimeter of the pool. After the place navigation test was finished on the 10th day, the platform was removed from the water tank. The time was spent in the target quadrant where the platform located was recorded for analysis. Mice were started in a position opposite the location of the platform position and allowed to swim for 60 s. During the test for 10 days, mice were treated daily with memantine (10, 20 mg/kg), MK-801 (10 mg/kg), or donepezil (0.3 mg/kg).

2.6. Open field test

The open field test fear response to novel stimuli was used to assess locomotion, exploratory behavior, and anxiety. Open field test protocols were modified (Lukacs et al., 1995). The open field test consisted of a wooden box (50 × 50 × 50 cm). A 10 cm area near the surrounding wall was delimited and considered the periphery. The rest of the open field was considered the central area. The distance traveled, the ratio of the distance traveled in the central area/total distance traveled, and the time in the center of the open field were analyzed as measures of anxiety-like behavior. During the test, mice were allowed to move freely around the open field and to explore the environment for 15 min.

2.7. Senescence-Associated ß-Galactosidase (SA-ßgal) Staining

PC12 cells and HUVEC were grown in 60-mm collagen-coated dishes to 80% confluence. PC12 cells were pretreated with vehicle (0.05% DMSO), memantine (100 μM), MK-801 (100 μM), or N-propyl-L-arginine (100 μM) diluted in RPMI 1640 medium for 1 day. HUVEC were pretreated with vehicle (0.05% DMSO) or memantine (100, 200 μM) diluted in EGM-2 medium for 1 day. PC12 cells and HUVEC were washed three times with the medium and then treated for 10 h with 10 mM glutamate diluted in medium. After treatment, PC12 cells were cultured with medium containing these compounds for 10 days. At 10 days after the start of treatment with glutamate, PC12 cells and HUVEC were fixed, and the proportion of SA-ßgal-positive cells was determined as described (Dimri et al., 1995).

2.8. Antibodies and immunoblotting

Cells were lysed on ice for 1 h in buffer (50 mM Tris–HCl, pH 7.6, 150 mM NaCl, 1% NP-40, 0.1% SDS, 1 mM dithiothreitol, 1 mM sodium vanadate, 1 mM phenylmethylsulfonyl fluoride, 10 μg/mL aprotinin, 10 μg/mL leupeptin and 10 mM sodium fluoride). After blocking, the filters were incubated with the following antibodies: anti-nNOS (BD Biosciences, San Jose, CA, USA), anti-p53, anti-SIRT1 (Santa Cruz Biotechnology, Inc., Santa Cruz, CA, USA), anti-NMDAR 2A, 2B (Abcam PLC, MA, USA), and anti-ß-actin (Sigma-Aldrich). After washing and incubation with horseradish peroxidase-conjugated anti-rabbit or anti-mouse IgG (GE Healthcare Life Sciences, Pittsburgh, PA, USA) for 1 h, the antigen-antibody complexes were visualized using an enhanced chemiluminescence system (GE Healthcare Life Sciences).

2.9. Measurement of Ach

The concentration of acetylcholine was measured with a choline/Ach quantification kit (BioVision, CA, USA) according to the manufacturer's instructions.

2.10. Detection for carbonylation of proteins

Carbonylation of proteins was detected using an Oxyblot protein oxidation detection kit (Millipore, MA, USA) according to the manufacturer's instructions.

2.11. Cell viability assays

Cell viability with glutamate (0–20 mM) for 5 h was assessed by using the 3-(4, 5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulphophenyl)-2 H-tetrazolium (MTS) assay (Promega, Madison, WI) in 96-well plates (20,000 cells/well) following the instructions of the manufacturer.

2.12. Data analysis

Values are shown as mean ± S.E.M in the text and figures. Differences between the groups were analyzed using one-way analysis of variance, followed by the Bonferroni test. Probability values less than 0.05 were considered significant.

3. Results

3.1. Glutamate-induced senescence of PC12 cells and memantine inhibited it

To investigate whether glutamate treatment induced cellular senescence, PC12 cells with neuronal differentiation induced by NGF were used. When PC12 cells were treated with 10 mM glutamate for 10 h, a large and flattened senescent appearance was observed and the number of SA-ßgal-positive cells was increased after 10 days of treatment (Fig. 1A and B). These results indicate that glutamate has the capacity to induce the senescence of PC12 cells. Next, when 200 μM memantine pretreatment for 1 day was performed before glutamate induction of senescent PC12 cells, the senescent appearance and the number of SA-ßgal-positive cells were decreased (Fig. 1A and B). To verify the changes in other proteins related to senescent phenotypes, SIRT1 and p53 expression were examined. Treatment with glutamate decreased SIRT1 expression and increased p53 expression; however, pretreatment with 100 or 200 μM memantine prevented these changes (Fig. 1C). These results indicate that pretreatment with memantine inhibited glutamate-induced the senescence of PC12 cells.

Memantine is a noncompetitive NMDA receptor antagonist. Therefore, to clarify the protective effect of memantine against cellular senescence via the NMDA receptor, PC12 cells were treated with another potent, selective noncompetitive NMDA receptor antagonist, MK801 (Benveniste et al., 1984). Similarly to memantine, pretreatment with 100 μM MK801 decreased the number of SA-ßgal-positive cells (Fig. 1D). These results indicate that memantine inhibited the senescence of PC12 cells through the NMDA receptor.

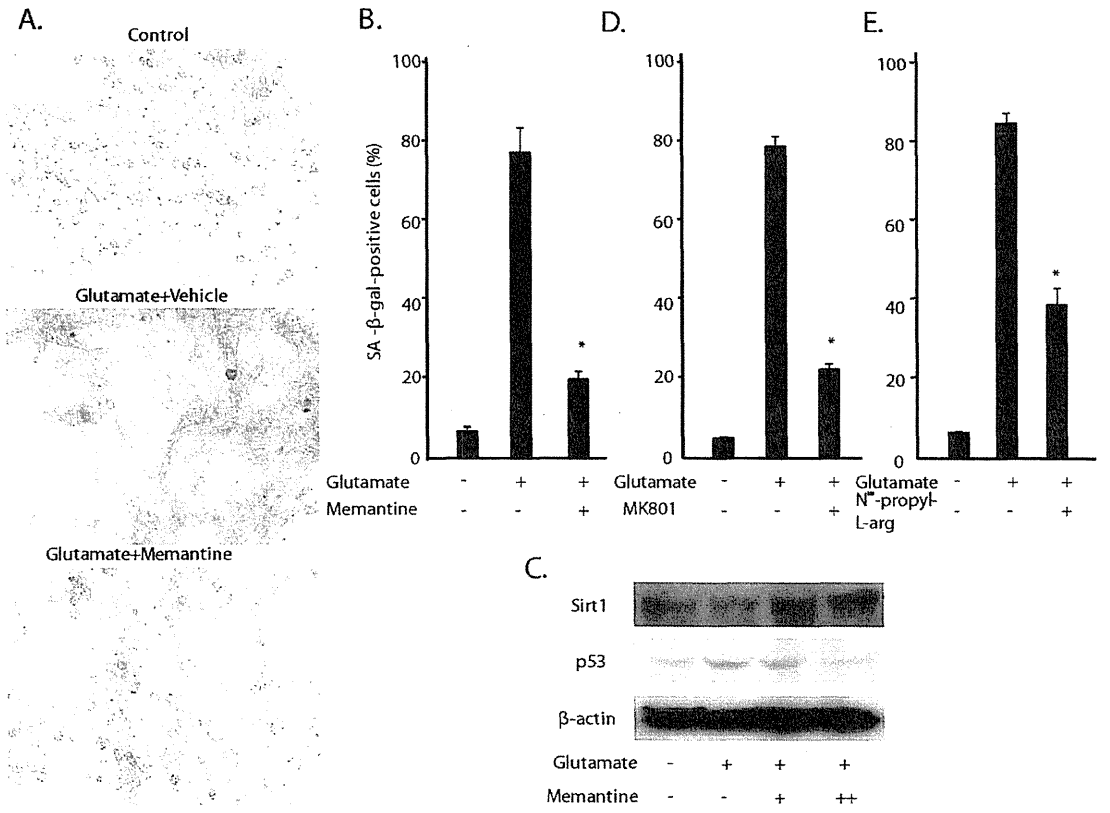

Fig. 1. A. Memantine (200 μM) inhibited SA-βgal activity and senescent morphological appearance induced by glutamate (10 mM). Percentage (%) of SA-βgal-positive PC12 cells with treatment with memantine (100 μM) (B), MK801 (100 μM) (D), or N^{ω}-propyl-L-arginine (100 μM) (E). (*$p < 0.05$, $N = 3$). C. Expression of SIRT1 and p53 in glutamate (10 mM)-treated PC12 cells under treatment with memantine (+: 100 μM, ++: 200 μM). ($N = 3$, representative shown).