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Substitute character or substitute part of one or more word(s)	through letter or through characters	new character or new characters
Change to italics	— under matter to be changed	ital
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アルコール依存症治療の現場から

樋口　進　独立行政法人国立病院機構 久里浜アルコール症センター 副院長

アルコール依存症とは

アルコール依存症者とは、医療の分野でも「酒で問題を起こす人」あるいは「酒がやめられない人」程度にしか理解されていないことが多い。この点を踏まえて、本稿ではまず、アルコール依存症の診断から話を始めることにする。

WHO（世界保健機関）によれば、アルコール依存症は「大切にしていた家族、仕事、自分の健康などよりも飲酒をはるかに優先させるような状態」と定義されている。日本の医療制度では、ICD-10（国際疾病分類第10版、2003年改訂）の診断分類が使用されており、アルコール・薬物依存症には共通した診断ガイドラインが示されている。

①物質摂取への強烈な欲求
②物質摂取行動の統制困難
③離脱症状の存在
④耐性の増大または大量使用
⑤物質摂取中心の生活
⑥有害な結果にもかかわらず物質使用

具体的には、上記6項目のうち3項目以上が同時に、診断日からさかのぼる12カ月間に一定期間（1カ月以上が目安）続くか、繰り返し起きていた場合に、依存症と診断される。アルコールの場合には、「物質」を「アルコール」に置き換えればよい。しかし、あいまいな表現が多いので、実際の診断に当たっては、解説書を使用する必要がある。

アルコール依存症のスクリーニング

日常の臨床でアルコール依存症をスクリーニングするために、スクリーニングテストが使われることがある。日本では、1970年代に標準化された久里浜式アルコール症スクリーニングテスト（KAST）が最も広く使われてきた。

表　新久里浜式アルコール症スクリーニングテスト（KAST-M※）

最近6カ月の間に、以下のようなことがありましたか

	項　目	はい	いいえ
1	食事は1日3回、ほぼ規則的にとっている	0点	1点
2	糖尿病、肝臓病、または心臓病と診断され、その治療を受けたことがある	1点	0点
3	酒を飲まないと寝付けないことが多い	1点	0点
4	二日酔いで仕事を休んだり、大事な約束を守らなかったりしたことがある	1点	0点
5	酒をやめる必要性を感じたことがある	1点	0点
6	酒を飲まなければいい人だとよく言われる	1点	0点
7	家族に隠すようにして酒を飲むことがある	1点	0点
8	酒が切れたときに、汗がでたり、手が震えたり、いらいらや不眠など苦しいことがある	1点	0点
9	朝酒や昼酒の経験が何度かある	1点	0点
10	飲まないほうがよい生活が送れそうだと思う	1点	0点
	合計点		点

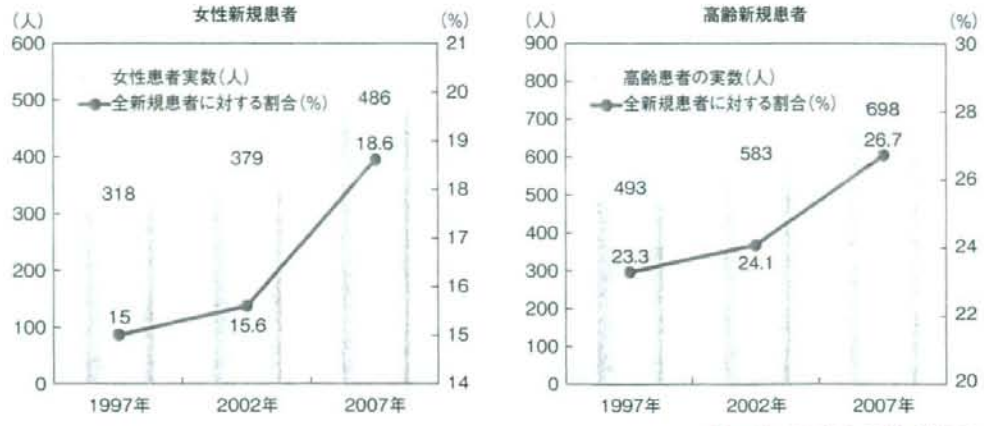
1. 合計点が4点以上
アルコール依存症の疑い群：アルコール依存症の疑いが高い群です。専門医療の受診をお薦めします。

2. 合計点が1－3点
要注意群：飲酒量を減らしたり、一定期間禁酒をしたりする必要があります。医療者と相談してください。ただし、質問項目1番のみ「いいえ」の場合には、正常群とします。

3. 合計点が0点
正常群

※KAST-F（女性版）は、久里浜アルコール症センターHP（http://www.kurihama-alcoholism-center.jp）を参照。

図　女性・高齢新規受診患者数および全新規患者に占める割合の推移



樋口　進：2007年度厚生労働科学研究

2007年、改定版（新KAST）が作成され、現在では男性版（KAST-M、表）と女性版（KAST-F）が用意されている。前者は10項目、後者は8項目の「はい・いいえ」で回答する質問からなる簡便なテストである。

実態および治療状況の推計

2003年に実施された厚生労働科学研究による成人の飲酒実態調査では、前記のICD-10診断ガイドラインに合致する依存症者は国内に約80万人存在すると推計された。また、KASTによる「アルコール依存症の疑いあり」とされた人は実に440万人存在した。約20年前の1984年にも、当センターが日米共同科学研究の一環として同種の疫学調査を実施した。その時に比べて、KASTによるアルコール依存症が疑われる人の割合は、男性では7.1%で不変であったが、女性では0.6%から1.3%と2倍以上に増えていた。

アルコール依存症の治療はほとんどの場合、精神科で行われている。2004年6月時点で、日本の精神病院入院患者約32万6100人のうち1万5400人（4.7%）がアルコール依存症者であった。これらのうち、一部の患者は依存症の治療プログラムが用意されている、いわゆるアルコール依存症専門治療施設で治療されている。厚生労働省によると、これら専門治療施設の病床数は現在約4200床程度しかないと推計されている。

専門治療施設における患者の特徴

最近、当センターで女性患者と高齢患者の増加が顕著である。他の施設でも同じような傾向が認められるかを確認するため、当センターを含めた11の専門治療施設を対象に調査を行った。これらの施設における1997年、2002年、07年の全新規患者数、女性新規患者数、高齢（60歳以上）新規患者数を調べた（図）。女性患者、高齢患者はいずれも、実数においても、また、全新規患者に対する比率においても明らかに増加していた。前記の疫学調査等からも示唆されるように、女性・高齢患者の増加は全国的な傾向であると言える。

また、04年から07年にかけて全国54の依存症専門治療施設に入院した約870人のアルコール依存症者の臨床的特徴、治療経過、治療転帰などについても調査した。結果の一部を紹介すると、まず91%が依存症で、12%に振戦せん妄、8%にうつ病、3%に健忘症候群が認められた。男女差は年齢構成、婚姻状況、合併精神・身体疾患等で認められた。女性は男性に比べて、より若年で、未婚者が少なく、離婚者が多く、精神疾患を合併している場合が多かった。また、60歳以上の高齢アルコール依存症者の約20%に、clinical dementia rating（CDR：臨床認知症評価法）による認知症の罹患が明らかになった。

久里浜アルコール症センターにおける治療

アルコール依存症の治療はどのように行われるのだろうか。一例として当センターにおける治療を取り上げる。当センターにおける治療の特徴の一つは、中年男性、女性、高齢者など対象が細分化され、それぞれに治療病棟と専用治療プログラムが用意されていることである。本稿では、この中の中年男性に対する一般的な入院治療を紹介する。

入院患者は、まず内科病棟で精神・身体合併症について評価され、評価結果に基づき必要な治療がなされる。検査の中には、血液・生化学検査、上部・大腸内視鏡検査、胸部CT、頭部MRI、脳波検査などが含まれる。離脱症状を示す患者には、抗不安薬（通常ジアゼパム）を用いて治療を行う。患者は全入院期間を通じて、1回1時間×24回からなる教育プログラムが義務付けられている。入院後間もなく、この教育プログラムと精神科医による治療的な介入が開始される。

内科病棟での約3週間の入院治療後、精神科のリハビリ病棟で約7週間の入院治療を行う。ここでの主要な治療は、既述の教育プログラム、小集団による認知行動療法、および医師による個人精神療法である。

このうち認知行動療法は、00年から開始された治療法である。患者が飲酒を続けるのは、彼らの飲酒に対する誤った認知によるものと考え、この修正を治療の目標とする。3～5人の患者に1人のリーダー（医師、ソーシャルワーカーなど）が割り当てられ、週ごとに決められたテーマについてグループワークを行い、全7回のセッションで治療を終了する。

当センターでは、アフターケアの3本柱として、退院後の定期的通院、ジスルフィラムなどの抗酒薬の服用、および断酒会やAA（アルコホーリクス・アノニマス）等の自助グループへの参加を推奨している。実際、これらの治療が行われた場合の治療転帰（通常は断酒率で評価）は良好である。

シリーズ 続・社会問題から見た 心の病 ～事例編⑦～

アルコール依存症

(独)国立病院機構久里浜アルコール症センター(神奈川県) 樋口 進副院長

かつてアルコール依存症と言えば，中年男性をイメージした。しかし，最近，臨床の場では女性や高齢者が台頭しており，このイメージが変貌しつつある。抑制を欠いた飲酒や離脱症状など，依存症としての症状に違いはないが，女性や高齢者の場合，依存症の背景やそこに至る経過に特徴が見られる。本稿では，臨床場面で遭遇する可能性の高い女性・高齢者のアルコール依存症例を提示し，その特徴について説明した。

女性症例を見たら摂食障害が隠れていると疑え

：36歳，女性

過食後の嘔吐を繰り返す

本人は，3人姉妹の長女として出生した。小学校から中学校にかけて，両親の不仲など家庭の問題のためか引っ込み思案となり，人との関係ではいつもおどおどしていたという。

小学校の高学年から太り始め，中学校2年生ころには，身長155cmで体重は65kg近くあったという。このころ，級友からのいじめに遭い，彼らを見返すつもりで極端なダイエットに走った。体重は40kg程度まで短期間に減少した。食行動はその後，拒食から過食後の嘔吐に変わっていった。

結婚後25歳時に妊娠したが，妊娠中毒症がひどく，病院にかかったところ，産科の医師からビールを飲むことを勧められた。産後もその習慣は続いた。

このころ，しゅうとめとの間がうまくいかず，そのストレスもあり，酒量は急速に増加した。低栄養と肝機能障害などで，当センターを初診する前に総合病院の内科に4回入院していた。

当センターのアルコール専門病棟に入院後，食行動について詳しく聞いたところ，過食していることが認められた。家族が寝静まった後に，多量に食べては吐くことをほぼ毎日繰り返しているとのことであった。恥ずかしいことなので，だれにも知られないようにしており，夫も主治医が説明するまでは本人の摂食障害を知らなかった。

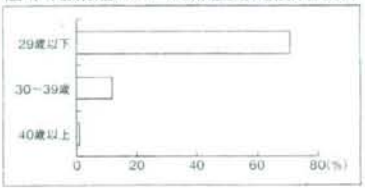
退院後1年ほどはジスルフィラム0.2gを使用し，自助グループのミーティングにも週1～3回ほど通っていた。自助グループには3年ほどで行かなくなったが，当センターには4週に1回の通院を続けている。退院後，現在まで11年間，完全断酒を継続している。

症例の背景には家族問題や精神科合併症

女性におけるアルコール依存症例の特徴は，背後に複雑な家族問題や精神科合併症などを抱えていることが多いことである。多くの場合，これらの問題は彼女たちが依存症に陥っていくのを助長しているように思われる。

精神科合併症では，うつ病や情緒不安定性人格障害と並び，摂食障害が非常に多い。少し古い資料だが，図1は当センターに入院した女性のアルコール依存症患者の摂食障害合併率である(文献)。

(図1) 年齢別女性アルコール依存症患者の摂食障害合併率



図のように，若ければ若いほど合併率が高く，初診時29歳以下では70%以上で摂食障害の合併が見られた。ほとんどの場合，過食を合併しており，摂食障害の後にアルコール依存という経過をたどる。

通常，飲酒問題が顕在化するころには食行動異常は慢性化しており，治療が難しいことが多い。これに比べれば，今回の症例のように断酒の達成は相対的にそれほど困難ではないようだ。

(文献)
Higuchi S, et al. Alcoholics with eating disorders: Prevalence and clinical course: a study from Japan. *Br J Psychiatry* 1993; 162: 403-406

定年退職後の依存症の増加が憂慮される

：68歳，男性

うつ症状を緩和するために大量飲酒

妻と娘2人の4人家族である。高校卒業後，いくつかの会社に勤めた後，25歳から同じ会社でサラリーマンを60歳の定年まで勤め上げた。元来，飲酒後に顔の赤くなるタイプで，酒には弱いほうであった。妻の記憶でも，27歳時に結婚後もしばらくは飲酒していなかったという。

その後，会社の付き合いなどで飲酒する機会が増え，50歳以降は1日日本酒3～4合程度は飲んでいた。定年後しばらくは同じような飲み方をしていたという。

62歳時，自宅を新築することになり，本人が不動産屋などと交渉に当たったが，建てた場所の日当たりが悪く，また，値段が割高なのが後でわかった。このことで，本人はかなり後悔したが，加えて家族からも繰り返し文句を言われ，親せきからも叱責を受けた。

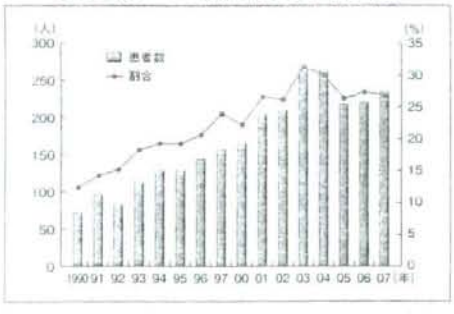
そのようなことが続いているうちに，うつ状態に陥った。以後，うつ症状を緩和するために酒量が急に増えた。

64歳時，うつ病の治療目的で他院を受診し，入院となった。2か月の入院でうつは改善したが，退院後に飲酒の再開とともに，飲酒問題が悪化した。朝から飲酒し，多いときは1日に1升近くも飲んだ。

飲酒して近くの公園で寝ていることや，転倒してけがをすることなどが頻繁に起きるようになったことから，65歳時に家族に連れられて当センターを受診し，入院となった。以後，当センターに3回入院している。

入院のたびに飲み方は悪化しており，大小便の失禁もするようになった。3回目の退院後デイケアが導入され，現在まで1～2回の短期間の飲酒エピソードがあるが，1年以上，断酒を続けている。

(図2) 高齢アルコール依存症初診患者数・割合の推移



定年退職などにより"たが"が外れて依存症的な飲み方に

図2は，当センターを新規受診した60歳以上の依存症者の実人数，および新規受診者全体に対する割合の変化を示している。図からは，高齢症例の増加がいかにすさまじいかが理解できると思う。高齢症例は，若年発症で高齢化したケースと，今回の症例のように高齢になってから発症したケースに分けられる。

一般に，後者のほうが前者に比べて，社会的安定性が高く，健康・社会的問題がより少なく，依存の程度もより低いと言われている。

高齢発症例の多くは，定年退職後発症するケースである。定年前，多量に飲酒はしているが，会社という枠組みで飲酒のコントロールがなされていた。

しかし，ひとたび退職すると，この"たが"が外れて，容易に依存症的な飲み方になるようだ。このケースのようにうつ病などが重なれば，発症のプロセスはさらに加速されることになる。

戦後のベビーブーマーが大量退職する今，このタイプの依存症の増加が憂慮される。

(続く)

飲酒だけでなく背景も考慮して断酒指導を

女性症例の治療に当たっては，飲酒問題だけでなく，その背後の問題にも注意を向けなければならない。強力な断酒指導に加えて，家族問題や精神科合併症に対する適切な薬物治療・精神療法が必要なことが多い。しかし，順序はまず断酒の達成であり，そのうえで上記の治療介入がなされるべきである。高齢者は若年者に比べて治療後の断酒達成率が高い傾向にある。なかでも，高齢発症例は治療によく反応することが知られている。高齢のために，家族らから治療をあきらめられがちであるが，断酒後のQOLの向上は目を見張る場合が多く，治療しがいがある。

●特　集●

地域で取り組むアルコール関連問題

ALCOHOL

わが国のアルコール関連問題の現状

独立行政法人 国立病院機構 久里浜アルコール症センター

遠藤光一 ＝写真

樋口　進

① はじめに

わが国ではアルコールは古来飲食物としてだけでなく、人間関係の手段として、広く人々に親しまれてきました。それでは、現在わが国ではどれくらいの人がお酒を飲んでいるのでしょうか？　国民健康・栄養調査（2005年）によると毎日飲酒する人の割合は男性で33・7％、女性で6・3％と報告されています。また男性では半数以上の人が週3日以上の飲酒をしています。年齢階級別にみれば、男性は40～60歳代の割合が高く、女性では30～40歳代の割合が高くなっています。また、1日60 g以上の飲酒をする多量飲酒者（日本酒換算で3合以上）の割合は、男性で13・2％、女性で4・0％と報告されています。

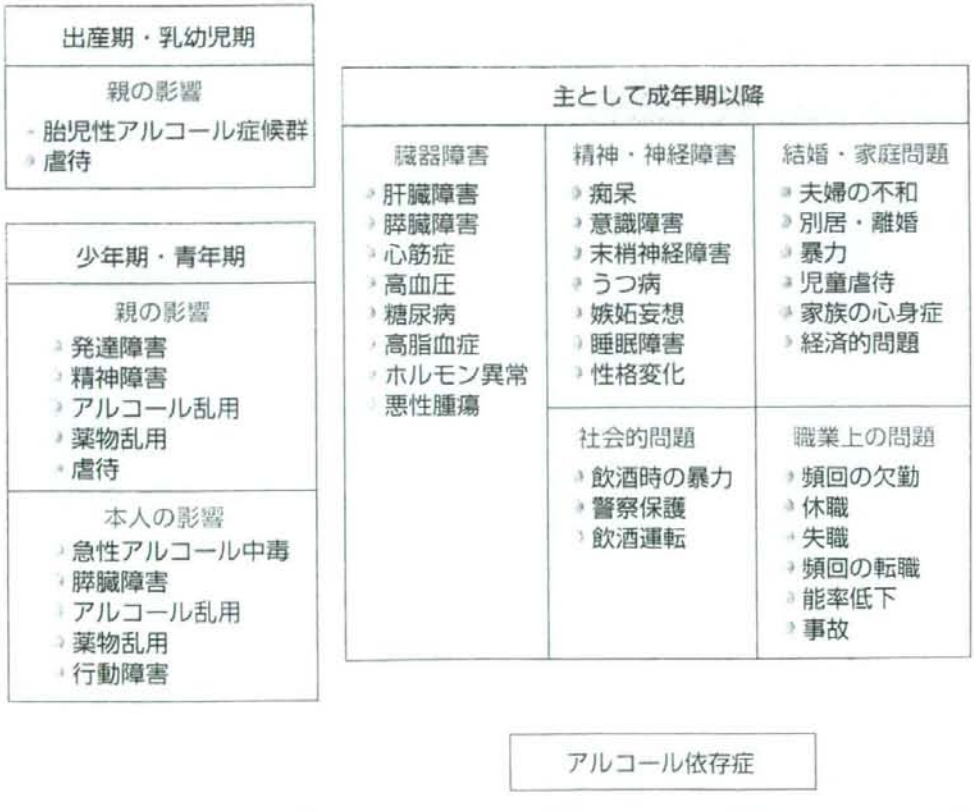
このように、近年の飲酒機会の増大、

多種多様なアルコール飲料の販売にともない、アルコールに関連する問題もその広がりと深刻の度を増してきています。アルコール関連問題というと、すぐに頭に浮かぶものはアルコール依存症でしょう。しかし、アルコール依存症はアルコール関連問題の一部にすぎません。飲酒による肝障害などの健康被害、飲酒運転による悲惨な交通事故など、アルコールに関連する問題を挙げるときりがありません。図1に主なアルコール関連問題を示しました[1]。

2 急性アルコール中毒

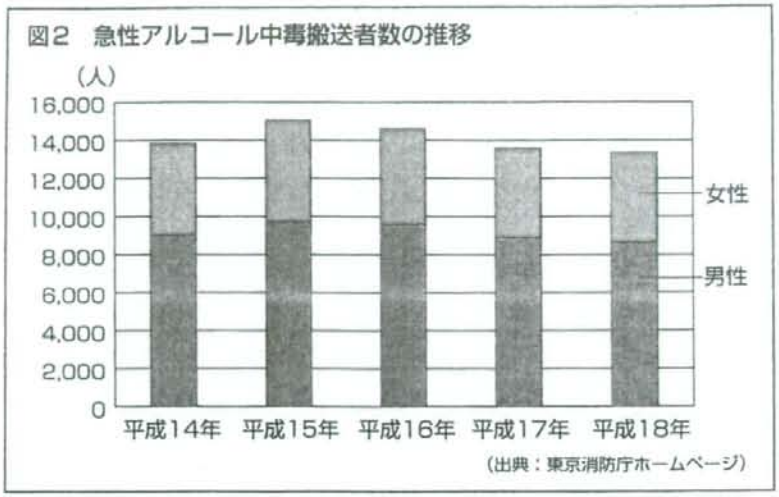
急性アルコール中毒は場合によっては死に至ることもあるため、重篤な関連問題の一つとして以前より指摘されてきました。これは、単純酩酊の延長線上にある意識障害とともに運動失調や嘔吐などが出現し、身体生命に危険

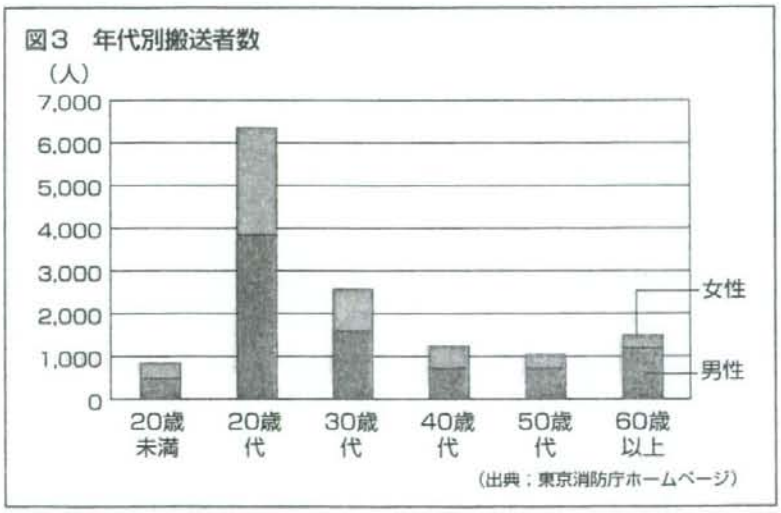
図1　アルコール関連問題



（出典：樋口進編：健康日本21推進のためのアルコール保健指導マニュアル、2003）

が迫った状態を指します。最近では、「イッキ飲み」による急性アルコール中毒が問題となっています。東京消防庁の統計では06年の急性アルコール中毒による搬送人員は1万3397人でした（図2）[2]。このうち54人が重症以上（生命の危険が強いと認められるもの）でした。





年齢別にみると10歳代で810人、20歳代で6267人となっており、10～20歳代で半数を超えていました（図3）[2]。これは大学生を中心とした若年者が、自己の飲酒量の限界を知らずにその場の雰囲気に流され、または強制的に飲酒させられた結果であると思われます。一般的に未成年者、女性、高齢者、飲酒後顔の赤くなる人などでは、急性アルコール中毒になる危険性が高くなることは知っておく必要があると思います。

3 臓器障害

図1に示したように飲酒による臓器障害は全身に及びます。

医療機関を訪れた患者さんや一般の人々に、飲酒に伴う疾患として最も知られているのは、肝臓の障害です。肝疾患に占めるアルコール性肝障害の比

率は以前に比べ増加しています。02年の調査では20%を超えるまでになりました[3]。

大量飲酒者ではまず、脂肪肝が起こります。これは毎日60～80gのアルコール（日本酒換算で3～4合）を摂取する人なら、誰でも起こり得る疾患です。脂肪肝の状態で大量飲酒を続けると、その約20%にアルコール性肝炎が発症すると言われています。アルコール性肝炎は、黄疸、発熱、嘔吐などの急激な症状を伴って発症し、ときに感染症や多臓器障害を併発し、重症化します。それでも大量飲酒を続けると肝硬変となります。肝硬変の主症状は黄疸、腹水、浮腫、出血傾向、意識障害（肝性脳症）などで、肝不全、消化管出血、感染症などの併発により、死に至ります。毎日100～120gのアルコール（日本酒換算で約5合）を15～20年間続けている人に多く発症すると言われています[4]。また、女性は男性に比べ、より少量、より短期間で肝障害を起こしやすいことも知られています。女性の社会進出の増加に伴い、今後は女性のアルコール性肝障害の増加が予想されています。

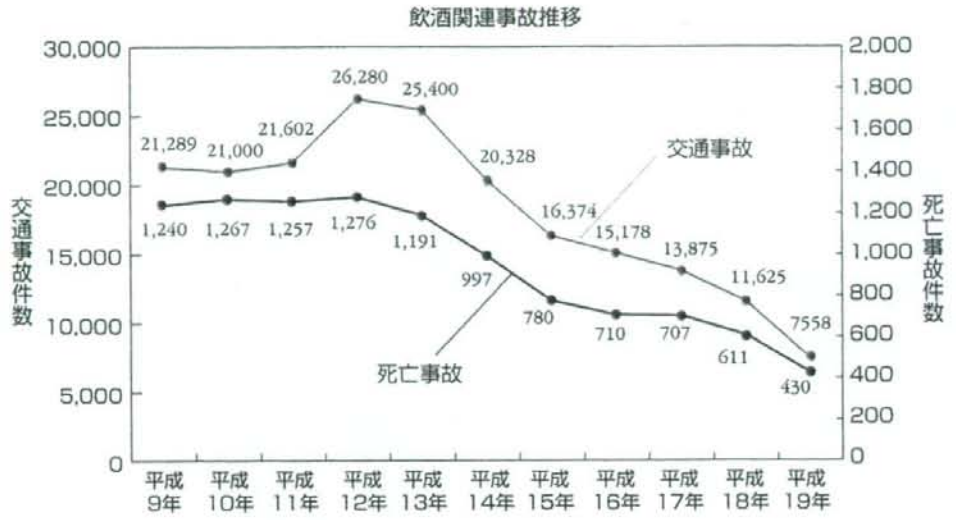
4 社会的問題

アルコール関連問題は医学的な側面だけでなく、社会的な側面からも大きな影響を及ぼしています。家庭の問題として、夫婦間の不和、離婚、暴力、児童虐待、子どもの精神・発達の障害、AC（アダルトチルドレン）など。職場の問題として、労働意欲の低下、頻回の欠勤、休職、失職、事故など。触法問題として、暴力、傷害などの犯罪、飲酒運転による物損事故、人身事故など。多岐にわたる問題が挙げられます。

ここでは特に飲酒運転について述べたいと思います。警察庁の統計（図4）[5]によれば、飲酒運転による交通事故件数は、02年6月に施行された改正道路交通法により罰則等が強化されたこともあり、00年（2万6280件）をピークに徐々に減少に転じ、07年では7558件にまで減少しています。同様に飲酒運転による死亡事故件数も減少してきており、07年では430件と10年前の約3分の1となっています。しかし、死亡事故率を飲酒有無別にみると、飲酒運転の死亡事故率は飲酒なしの9・4倍であり、酒酔い運転にあっては、34・4倍と高く、飲酒運転による交通事故が死亡事故につながる危険性は依然として高いことが示されています。

06年8月に福岡市で幼児3人が犠牲となる悲惨な飲酒事故が起こりました。それを契機に飲酒運転撲滅の機運が高まってきたにもかかわらず、その後も

図4　飲酒運転による交通事故件数の推移



（出典：警察庁ホームページ）

飲酒運転による死亡・重大事故は後を絶ちません。飲酒運転事故を起こした運転者では、過去にも飲酒事故・違反の前歴がある人の割合が、飲酒運転事故以外の運転者の前歴率に比べ高いといわれています。それらの人は、飲酒運転を日常的に繰り返している可能性があり、背景に多量飲酒、アルコール依存症の存在が疑われます。そのため、罰則の強化など厳罰化のみでは飲酒運転はなくならないでしょう。多量飲酒やアルコール乱用・依存への対策に踏み込んだ更なる対策が期待されます。

5　おわりに

以上述べてきましたように、アルコール関連問題は多岐にわたります。飲酒問題への保健指導というと、アルコール依存症を思い浮かべ二の足を踏む方も多いでしょう。しかし、冒頭でも述べましたようにアルコール依存症はアルコール関連問題の一部に過ぎません。その周囲に広がるアルコール関連問題を減らしていくことが、現在一番求められていることであり、ひいてはアルコール依存症者を減らすことになるのです。

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●お酒のコラム●

アルコール発酵と口噛み酒

（編集部）

お酒の種類は日本酒、焼酎、ビール、ウイスキー、ワインなどいろいろあるが、つくり方の基本は同じ。微生物の働きで糖が発酵し、アルコール分を含んだ「酒」になるというものだ。

「聖書」にもたびたび登場するブドウ酒（ワイン）は最も古い酒といわれ、紀元前6000年ごろの古代メソポタミアにはすでに存在したという。ブドウは自然界でも放っておくと、時間が経てば果糖が発酵し、お酒のようになる。ブドウの皮には果糖をアルコールに変える酵母が付着しているためだ。かつては自然発酵が主流だったが、現在では特別に培養した酵母を添加し、酸化防止剤なども使用されている。

一方、米や麦はそのままでは発酵しない。そのため日本酒やビールでは、でんぷん質をアミラーゼによって糖に変える「糖化」という工程が必要になる。日本酒の場合は麹（こうじ）が糖化の役割を果たしている。

『古事記』にはコノハナサクヤヒメが米を噛んで酒をつくったという記述がある。唾液中のアミラーゼがでんぷん質を糖化させ、いったん口から吐き出して空気に触れさせることで、野生の酵母菌が糖を発酵させてアルコールを生成するからだ。これを「口噛み酒」という。米だけでなく、トウモロコシや木の実など、でんぷん質を含んだ食物を噛むことでつくられる。古（いにしえ）の時代、神事の際には口噛み酒がつくられ、原料を噛む役は巫女や処女が担ったという。「醸す」という言葉は「かむ」から派生したという説もある。

現代の衛生観念からいえば、受け入れがたいことだが、南米やアジア、アフリカの一部では、今でもこの“製法”が行われているという。

参考：『食物誌』（中央公論社）、『別冊歴史読本 日本人と酒』（新人物往来社）ほか

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Alcohol intake and quantitative MRI findings among community dwelling Japanese subjects

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ABSTRACT

Background and purpose: The relationship between alcohol consumption and subclinical findings on magnetic resonance imaging (MRI) remains uncertain. We examined the relationship between light to moderate alcohol intake and silent brain infarction (SBI), white matter lesions (WMLs), and cerebral atrophy.
Methods: Cranial MRI was performed on subjects ≥40 years residing in a rural community in Japan (n=385; mean age, 67.2). Alcohol intake and type was determined using a detailed questionnaire; subjects were categorized into three groups: non-drinkers, light drinkers (<7 drinks per week), and moderate drinkers (≥7 drinks per week). Former drinkers were considered non-drinkers. Periventricular WMLs, deep WMLs and cerebral atrophy were measured quantitatively using a computer-assisted processing system (%PVWML, %DWML, and %Brain, respectively).
Results: Compared with non-drinkers, the prevalence odds ratios for SBI were significantly higher in light and moderate drinkers, after multivariate adjustment. After adjusting for age, sex, and other related factors, the geometric mean %PVWML volumes in light and moderate drinkers were 1.27% and 1.52%, respectively, significantly larger than those for non-drinkers (0.95%). The geometric mean %DWML volume in light drinkers was 0.10%, which was larger than the value for non-drinkers (0.06%); the value for moderate drinkers (0.13%) was significantly larger than that for non-drinkers. The geometric mean %Brain values for non-, light, and moderate drinkers were 92.1, 91.9 and 90.8%, respectively; a statistically significant difference was found between non-drinkers and moderate drinkers.
Conclusions: The present study indicates that regular drinking, including even low levels of consumption, may be a risk factor for subclinical findings detected on MRI in community-dwelling Japanese people.

1. Introduction

Alcohol intake has been proposed as a factor that increases the risk of hemorrhagic stroke in a dose-dependent manner [1,2]. In contrast, a J- or U-shaped association between light to moderate alcohol consumption and the risk of ischemic stroke has been found in several epidemiologic studies[1–5]. A meta-analysis of 35 observational studies revealed that heavy alcohol consumption increases the relative risk of stroke, whereas light or moderate alcohol consumption protects against ischemic stroke [2]; however, some reports demonstrate positive or no association of low to light to moderate alcohol consumption and ischemic stroke [6–8], and the influence of light to moderate alcohol intake on ischemic stroke is uncertain. In addition, the effect of alcohol on stroke is proposed to vary with race. Camargo reviewed 62 epidemiological studies and found that a J-shaped association has been found in predominantly white populations, while little association has been found among Japanese subjects [1].

Subclinical findings of the brain, such as silent brain infarction (SBI), white matter lesions (WMLs), and brain atrophy, can be visualized using magnetic resonance imaging (MRI). These findings are commonly seen in healthy elderly people and draw attention as an important prodromal stage or a risk for progression into symptomatic stroke and dementia [9–11]. We also have previously reported that cognitive impairment in non-demented elderly subjects was related to the presence of SBI, WMLs, and brain atrophy [12,13]. Therefore, to evaluate the effects of alcohol intake on the brain it is useful to investigate the relationship between alcohol intake and subclinical findings detected on MRI, yet few studies have examined these relationships. The Cardiovascular Health Study (CHS) found that among older adults,

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low to moderate alcohol consumption is associated with a lower prevalence of infarcts and WMLs, compared to non-drinkers and former drinkers, but with a dose-dependent higher prevalence of brain atrophy [14]. In contrast, The Atherosclerosis Risk in Communities (ARIC) study showed that alcohol intake was neither a risk factor for nor protective against MRI infarction and WMLs in middle-aged adults [15].

In the present study, we examined how drinking habits are related to SBI, WMLs, and brain atrophy in community-dwelling Japanese people, based mainly on a quantitative measurement method described previously [12].

2. Materials and methods

We examined volunteers ≥40 years of age (n=385; 149 men and 236 women; mean age, 67.2 [SD 11.8] years) living in the rural community of Sefuri village, Saga, Japan from August 1998 to November 2001 (the total population of the village was 1938 as of November 1999). Clinical information was gathered by means of a personal interview, and all subjects had no past history of stroke or transient ischemic attack (TIA). Each subject underwent standardized evaluations, including physical and neurological examinations, electrocardiogram (ECG), and a complete blood chemistry panel. Our study was approved by an institutional review committee and each subject gave informed consent. The study protocol was in accordance with institutional guidelines.

Blood pressure was measured in the sitting position by the standard cuff method after 5 min rest. Arterial hypertension was considered present if a subject had a history of repeated high blood pressure recordings of ≥160/95 mmHg or was being treated for hypertension for the purpose of measuring the long-term effects of moderate hypertension. Left ventricular hypertrophy (Minnesota Code 3-3-2), ST depression (4-1), or atrial fibrillation (8-3-2) was registered on 12-lead ECG recordings. Diabetes mellitus was defined as fasting plasma glucose greater than 7.77 mmol/l or a previous diagnosis of diabetes mellitus. Hyperlipidemia was defined as total serum cholesterol concentration >5.69 mmol/l or if the subject was being treated for hyperlipidemia at the time of examination.

We obtained information about typical alcohol intake and type of alcohol consumed from a detailed questionnaire. Weekly alcohol consumption was calculated by combining the amount of ethanol per day and frequency per week. We defined a drink as 10 g of ethanol, calculated as follows: 350 ml beer as 1.4 drinks, 180 ml sake (rice wine) as 2.2 drinks, 180 ml shochu (white spirits) as 3.6 drinks, 60 ml whiskey as 2.0 drinks, and 120 ml wine as 1.2 drinks. We categorized participants into three groups: non-drinkers who drank less than once a month, light drinkers (<7 drinks per week), and moderate drinkers (≥7 drinks per week). About half of the moderate drinkers (n=58) consumed ≥14 drinks per week. Former drinkers were considered non-drinkers in the present study.

MRI was performed on a 1.0 T superconducting magnet (MAGNEX alpha, Shimadzu, Kyoto, Japan) using the spin echo technique and fluid attenuated inversion recovery (FLAIR) sequences. Transverse T1-weighted (TR/TE 380/14 ms), T2-weighted (TR/TE 3750/110 ms), and FLAIR (TR/TI/TE 5800/1700/110 ms) images were obtained with a slice thickness of 6 mm separated by a 1-mm interscan gap. All scans were reviewed by two independent investigators who were blinded to all clinical data. The MRI data were modified from 256×256 pixels to 512×512 pixels and then transferred to a Macintosh computer. The area of WMLs and the brain volume were measured quantitatively using a computer-assisted processing system (NIH Image version 1.63), as described previously [12]. WMLs were defined as areas of high signal intensity on T2-weighted images that were isointense with normal brain parenchyma on T1-weighted images. WMLs that connected to the lateral ventricle were labeled as periventricular WMLs (PVWMLs), otherwise as deep WMLs (DWMLs). All measurements were performed using FLAIR images obtained at the level two slices above the pineal body. The area of PVWMLs and DWMLs was measured quantitatively using a semi-automatic method that counted the number of pixels with a given intensity. To correct for individual differences in head size, WMLs measurements were calculated as a percentage of the total intracranial volume. These findings were defined as %PVWMLs and %DWMLs.

The area of the cerebral parenchyma was quantified using T2-weighted images and was divided by the area inside the skull to calculate the %Brain value, which was used as an index of cerebral atrophy. %Brain was measured in four slices: at the level of the pineal body, at one slice and two slices above the pineal body, and at one slice below. The mean of these four values of %Brain was calculated. Diagnoses of SBI were made using the following qualitative criteria: (1) lesions with an abnormal signal in vascular distribution and no mass effects, and lesions 3 mm in size or larger defined as areas of low signal intensity on the T1-weighted images and high signal intensity on the T2-weighted images; and (2) a lack of neurological signs and/or symptoms that could be explained by MRI lesions. A diagnosis of SBI was made only when both researchers were in agreement.

Statistical analysis was carried out using the SPSS software package (SPSS Advanced Statistics TM version 6.1, SPSS Inc, Chicago, IL, USA). The distributions of %PVWMLs, %DWMLs, and %Brain approximated normal distributions only after logarithmic transformation. Therefore, the logarithmic transformations were performed before analysis using the following calculation method: log(%PVWMLs), log(%DWMLs+0.1), log(100−%Brain), and geometric means were reported as the mean of the volume and 95% confidence interval (95% CI) [16]. Univariate analysis was performed with ANOVA for continuous variables and the x^2 test for categorical variables. Forward stepwise logistic regression models were used to estimate the odds ratio (OR) of SBI for the alcohol intake categories, and stepwise multiple regression analyses were used to identify any variables associated with %PVWMLs, %DWMLs, and %Brain. We chose age, sex, body mass index, hypertension, diabetes mellitus, hyperlipidemia, history of coronary heart disease, abnormal ECG, current smoking, packed cell volume, and albumin as candidates for entry into both forward stepwise logistic regression analyses and stepwise multiple regression analyses. In addition, the three alcohol-intake categories were treated as two dummy-coded variables that represented light and moderate drinkers with non-drinkers as the referent group in multivariate analysis. The adjusted means (95% CI) of %PVWMLs, %DWMLs, and %Brain were continuously compared among the three alcohol-intake categories using ANCOVA. Variables adjusted in ANCOVA were those considered statistically significant in stepwise multiple regression analyses.

3. Results

Of the 385 subjects free of stroke or transient ischemic stroke, SBIs were seen in 43 subjects (11.2%), with a mean number of 1.5 infarcts; 41 of 43 subjects (95.3%) had lacunes (<15 mm). The geometric means of the %PVWML and %DWML volumes were 1.18% and 0.08%, respectively. The geometric mean volume of %Brain was 91.7%. Table 1 shows the clinical characteristics of the study subjects according to alcohol consumption. Univariate analysis demonstrated that age and sex ratios were significantly different among the three groups, as were hypertension, history of coronary heart disease, current smoking, systolic blood pressure, diastolic blood pressure, packed cell volume, total cholesterol, and HDL cholesterol.

To explore the reliability of the assigned drinking category, we examined mean HDL cholesterol levels according to alcohol-intake category, in accordance with the known relationship between alcohol consumption and HDL levels. After adjusting for age and sex, the mean values of HDL cholesterol in light and moderate drinkers were 1.60 mmol/l (95%CI 1.52–1.68) and 1.63 mmol/l (95%CI 1.54–1.72), respectively, which were significantly higher than the value for non-drinkers (1.44 mmol/l, 95%CI 1.38–1.50).

Table 1
Mean values or frequencies of characteristics of the study subjects according to alcohol-intake category

	Non-drinkers	Light drinkers	Moderate drinkers	P
	(n=176)	(n=100)	(n=109)	
Age, years	63.0±9.4	59.2±9.7	61.7±10.2	0.0078
Male sex, %	12.5	29.0	89.9	<0.0001
Body mass index, kg/m^2	23.1±3.4	22.7±3.1	23.5±3.2	0.1887
Hypertension, %	25.0	14.0	34.9	0.0023
Diabetes mellitus, %	2.3	6.0	8.3	0.0651
Hyperlipidemia, %	18.2	11.0	11.9	0.1751
History of coronary heart disease, %	5.1	1.0	9.2	0.0290
Abnormal ECG[a], %	6.8	6.0	13.8	0.0713
Current smoking, %	5.7	11.3	35.1	<0.0001
Systolic blood pressure, mmHg	137.4±23.1	128.6±22.7	138.0±21.2	0.0026
Diastolic blood pressure, mmHg	77.8±10.2	77.2±9.9	82.6±9.5	<0.0001
Fasting blood glucose, mmol/l	5.22±1.41	5.45±1.48	5.54±1.35	0.1569
Packed cell volume	39.3±4.0	40.6±3.6	43.4±4.5	<0.0001
Total cholesterol, mmol/l	5.20±0.84	4.97±0.83	4.91±0.88	0.0089
HDL cholesterol, mmol/l	1.48±0.35	1.61±0.35	1.55±0.46	0.0239
Albumin, g/l	4.4±0.2	4.3±0.2	4.3±0.3	0.7033

ECG indicates electrocardiogram. Values are mean±SD or percentage of subjects.
[a] Left ventricular hypertrophy, ischemic change, or atrial fibrillation.

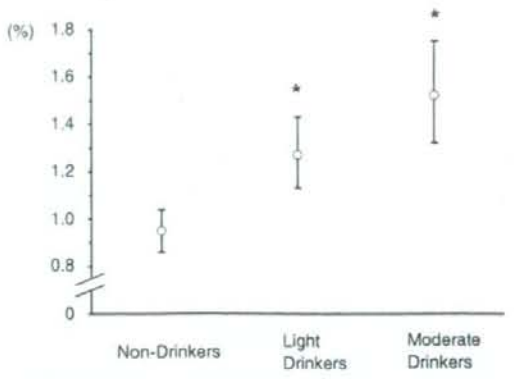

Fig. 1. %PVWML (periventricular white matter lesion) volumes according to alcohol-intake category. The graph shows geometric mean values in %PVWML and 95%CI. % PVWML was adjusted for age, sex, hypertension, and abnormal ECG. *P<0.05 versus non-drinkers.

Table 2 shows that compared with non-drinkers, the OR of SBI was 4.1 (95%CI 1.7–10.0, p=0.002) in light drinkers and 3.1 (95%CI 1.3–7.0, p=0.008) in moderate drinkers, after adjusting for age and hypertension selected by forward stepwise logistic regression analysis.

Stepwise multiple regression analyses revealed that light drinking, moderate drinking, age, sex, hypertension, and abnormal ECG were significantly related to %PVWMLs; furthermore, the same variables were related to %DWMLs. Moderate drinking, age, sex, and abnormal ECG were significantly related to %Brain.

The geometric mean %PVWML volumes for light and moderate drinkers were 1.27% (95%CI 1.13–1.43) and 1.52% (95%CI 1.32–1.75), respectively, which were significantly larger than the 0.95% (95%CI 0.86–1.04) value in non-drinkers after adjustment for age, sex, hypertension, and abnormal ECG (Fig. 1). The geometric mean %DWML volume in moderate drinkers was 0.13% (95%CI 0.09–0.18), which was significantly larger than the value of 0.06% (95%CI 0.04–0.08) in non-drinkers after adjustment for age, sex, hypertension, and abnormal ECG; the value of 0.10% (95%CI 0.07–0.13) in light drinkers was larger than that in non-drinkers, although the difference was not statistically significant (p=0.10), indicating that the effect of light alcohol intake on DWMLs is less than that on PVWMLs (Fig. 2).

No difference was found between the geometric mean %Brain volume in light drinkers (91.9%; 95%CI 91.4–92.4) and that in non-drinkers (92.1%; 95%CI 91.7–92.6); the value of 90.8% (95%CI 90.1–91.5) in moderate drinkers was significantly smaller than that in non-drinkers after adjustment for age, sex, and abnormal ECG (Fig. 3).

Table 2
Relative risk of silent brain infarction according to alcohol-intake category

	Odds Ratio	95% Confidence Interval
Non-drinkers (n=176)	1.0	-
Light drinkers (n=100)	4.1	1.7–10.0
Moderate drinkers (n=109)	3.1	1.3–7.0

Model was adjusted for age and hypertension selected by forward stepwise logistic regression analysis.

Excluding those who consumed ≥14 drinks per week from the moderate drinkers did not significantly change the results.

4. Discussion

Among community-dwelling elderly subjects, light to moderate alcohol intake increased the risk of SBI and WMLs, while moderate drinking was associated with brain atrophy.

Two previous studies have investigated the effects of light to moderate alcohol intake on subclinical MRI findings [14,15]. The CHS found that light to moderate alcohol consumption in older adults aged ≥65 years was inversely associated with the presence of MRI infarction and WMLs [14]; however, the ARIC study found that alcohol intake was not associated with MRI infarction or WMLs in middle-aged adults [15]. The differing results of these two studies in the USA may reflect the different ages of the subjects. The mean age of the subjects in the present study (67.2 years) is intermediate between those of these prior studies. One possible explanation for the lack of a beneficial effect of light to moderate drinking in the present study may be that the subjects in the present study are approximately ten years younger than those in the CHS.

In the present study, light to moderate alcohol intake increased the risk of SBI and WMLs in older adults. Discrepancies between the

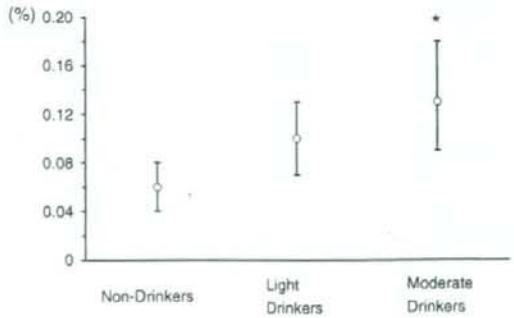

Fig. 2. %DWML (deep white matter lesion) volumes according to alcohol-intake category. Graph shows geometric mean values in %DWML and 95%CI. %DWML was adjusted for age, sex, hypertension, and abnormal ECG. *P<0.05 versus non-drinkers.

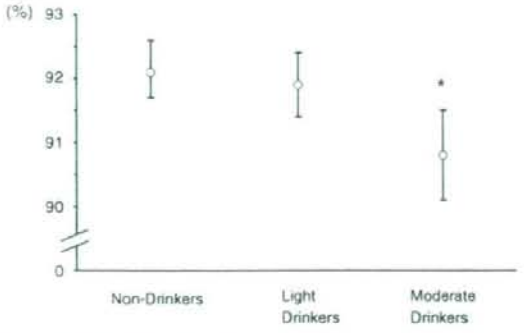

Fig. 3. %Brain volume according to alcohol-intake category. Graph shows geometric mean values in %Brain and 95%CI. %Brain was adjusted for age, sex, and abnormal ECG. *$P<0.05$ versus non-drinkers.

results of our study and those of the CHS may be partly explained by racial differences. The Japanese are a lighter-weight population compared with Western populations. For a similar alcohol dose, a higher blood alcohol level is expected in a low-weight population compared to a heavy-weight population. In addition, approximately 50% of the Japanese population is affected by a genetic deficiency in aldehyde dehydrogenase (ALDH) isozyme 2, which rapidly metabolizes acetaldehyde, the major oxidized product of alcohol; this defect is not present in the majority of Western populations [17]. It is possible that these factors cause the Japanese to be more susceptible to alcohol than Western populations. Camargo explained the relation between moderate drinking and ischemic stroke in terms of race: a J-shaped association has been found in predominantly Caucasian populations, while little association has been found among Japanese [1]. Furthermore, Camargo speculated that the racial difference in alcohol effects might be due to a more protective effect on the proximal segment of the cerebrovascular tree. The Japanese population has a higher incidence of intracranial small artery atherosclerosis than Caucasian populations, which have shown an inverse relation of moderate alcohol intake with atherosclerosis of the large arteries, but not with arteriosclerosis of the small intracerebral arteries [18].

The CHS and ARIC study showed that alcohol intake contributed to brain atrophy in a dose–response fashion [14,15]. The present study found that moderate drinking was associated with brain atrophy, but that light alcohol intake did not affect brain volume. Compared with the results of the CHS and ARIC study, the result of brain atrophy with light alcohol intake contradicts the findings for SBI and WMLs in the present study. The reason for this contradiction is not clear, but it is possible that our brain-atrophy measurement method may have had an influence on the result. In calculating the degree of brain atrophy, we quantified the entire area of the cerebral parenchyma and divided this by the corresponding areas inside the skull. Given that alcohol-related brain damage is known to affect the frontal lobes [19–21], our methods might be insufficient in evaluating focal cerebral atrophy.

We used a quantitative MRI method to investigate WMLs and brain atrophy, whereas the CHS and ARIC study semiquantitatively assessed abnormalities on MRI images [14,15]. We have previously shown the quantitative MRI method to be a useful tool in quantifying MRI abnormalities [12], and we employed this method because quantitative data enables us to undertake evaluations objectively. In addition, we assessed PVWMLs and DWMLs separately. Although light to moderate alcohol intake appeared to influence WMLs, it had a pronounced effect upon PVWMLs. PVWMLs and DWMLs are reported to differ in terms of their pattern of vascularization. As the vascular supply to PVWMLs is inferior to that of DWMLs under physiological circumstances, PVWMLs is especially vulnerable to a decrease in cerebral blood flow (CBF) [22,23]. Given that alcohol is reported to lead to reduced CBF [24–26], this reduced CBF may lead to a stronger relationship between alcohol intake and PVWMLs than that with DWMLs.

The mechanisms that underlie the association between alcohol intake and abnormalities on MRI images remain unclear. It is primarily thought that hypertension contributes to these abnormalities. Ohmori et al. demonstrated that alcohol intake, even light drinking, is a predictor of future hypertension among the Japanese population [27], and hypertension is reported to be related to SBI, WMLs, and brain atrophy [23,28–31]; however, as associations between alcohol intake and MRI findings were recognized after adjustment for hypertension, we should consider other mechanisms such as alcohol-induced cardiomyopathy and reductions in CBF [25]. Interestingly, plasma homocysteine levels were found to rise with moderate alcohol consumption in social drinkers [32]. We and others have reported the relationship between homocysteine levels and SBI [33,34], and some studies have demonstrated that homocysteine levels are associated with WMLs and brain atrophy, independent of other cerebrovascular risk factors [34–36].

The present study has some potential limitations. First, the validity of self-reported alcohol consumption has been debated [37]. However, the HDL cholesterol levels adjusted for age and sex among the three alcohol-intake groups in the present study may support the validity of the assigned drinking category. Second, in the present study, ex-drinkers were not excluded from the non-drinking group. Ex-drinkers may have ceased alcohol consumption because of health problems, and they are at increased risk of cerebrovascular disease [2,7,8]. Therefore, we may have overestimated the risk of abnormal MRI findings in non-drinkers, and as a result underestimated the risks of light to moderate alcohol intake. Namely, in contrast to studies showing reduced risk from light to moderate drinking, including ex-drinkers in the present study strengthens the conclusion that light to moderate drinking does not confer protection. Finally, the number of female participants in this study was greater than that of male participants. As some reports suggest that alcohol intake is detrimental to women at lower levels of consumption than for men [38], it is possible that the sex difference in the number of participants influenced the results.

In conclusion, the results of the present study suggest that regular drinking, including even low levels of consumption, is a risk factor for subclinical findings detected on MRI in community-dwelling Japanese people.

Acknowledgements

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Cognitive Consequences of Multiple Lacunes and Leukoaraiosis as Vascular Cognitive Impairment in Community-Dwelling Elderly Individuals

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The aim of our study was to investigate the effects of silent brain lesions on cognitive function of community-dwelling elderly individuals. Brain magnetic resonance imaging and other medical examinations were performed on 350 nondemented elderly individuals (121 male and 229 female, average age 72.4 years) who resided in the rural community of Sefuri Village, Saga, Japan. The mini mental state examination and modified Stroop test (MST) were used to identify cognitive impairment. White matter lesions (WMLs) and cerebral atrophy on magnetic resonance imaging were measured quantitatively. Multivariate analyses were done using a logistic regression model with a software package. Cognitive impairment defined by mini mental state examination score less than 24 was present in 55 individuals (15.7%). They had a lower educational level, significantly larger quantity of WMLs, and more remarkable cerebral atrophy. Frontal lobe dysfunction was detected in 52 individuals (14.9%) through prolonged MST score (>36 seconds). Impaired frontal lobe function was related to number of silent lacunar infarcts, larger WMLs, and more prominent cerebral atrophy. MST score in individuals with two or more infarcts was significantly more prolonged compared with MST score in those without infarction. These results suggest that WMLs may cause rather diffuse cognitive decline, whereas multiple lacunar infarcts are specifically involved in frontal lobe dysfunction. Silent ischemic lesions in apparently healthy elderly individuals seem to form a distinctive group of people with vascular cognitive impairment without dementia. This group should be the primary target of prevention of vascular dementia. **Key Words:** Asymptomatic stroke—lacunar infarction—white matter lesions—vascular dementia—neuropsychology—magnetic resonance imaging.

An increase in dementia is inevitable in an aging society, and the frequency of dementia in those older than 60 years has been doubling every 5 years, estimated to be present in a third of the population of 85-year-olds.[1,2] Although the main cause of dementia in the very old is Alzheimer's disease,[1,2] vascular dementia is apparently more preventable than Alzheimer's disease. However, not only has the diagnostic criteria for vascular dementia been equivocal, but the whole concept of the disease itself has remained under debate. Requirement of severe cognitive impairment or dementia prevents identification of early or treatable cases, and the emphasis on dementia distracts focus from prevention and treatment. Hence, Hachinski and Bowler[3] proposed that the term "vascular dementia" should be replaced with "vascular cognitive impairment" (VCI),[4] which encompasses all cases of cognitive impairment of cerebrovascular origin without

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a requirement for dementia. A further important point is that a preclinical phase may exist in VCI that differs from that in Alzheimer's disease,[5] which does not include neuroimaging data.

Neuropsychological profile in patients with stroke and transient ischemic attack has been characterized by disturbance of frontal lobe functions,[6] but this study did not include patients with VCI from other settings (e.g., nondemented community-dwelling individuals). In the Canadian Study of Health and Aging, a prospective cohort study of community- and institutional-dwelling persons, VCI without dementia (VCIND) was the most prevalent form of VCI (2.6% of those aged ≥ 65 years).[7] Although VCI is apparently not a single condition, its primary types of brain lesions are silent infarction, ischemic white matter lesions (WMLs), or both.[8] There is a generally accepted agreement that the most universally recognized lesions on magnetic resonance imaging (MRI) in healthy elderly people are WMLs or leukoaraiosis and silent infarction. Moreover, recently there has been a re-emphasis on the impact of brain atrophy on cognitive function in the general public.[9] Therefore, in the current study, we examined the effects of silent stroke, WMLs, and brain atrophy on cognitive function in community-dwelling people.

Methods

Between June 1997 and October 2001, we examined 350 elderly volunteers aged ≥ 60 years, living in the rural community of Sefuri Village, Saga, Japan. All volunteers were living independently at home without apparent dementia based on the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*.[10] Anyone with chronic intracranial illness including symptomatic cerebrovascular disease, psychiatric disorders including depression, or a history of head trauma were excluded. No participants showed apparent dysarthria or aphasia. This study was approved by the local ethics committee, and written informed consent was obtained from all participants.

Participants underwent a structured clinical interview regarding their history of cardiovascular disease, hypertension, diabetes mellitus, and hyperlipidemia, and their smoking habits and alcohol consumption. In addition to height, weight, blood pressure measurements, and a neurologic examination, the testing categories included general hematology tests, biochemistry tests, and electrocardiograms.

All participants underwent neuropsychological tests (the mini mental state examination [MMSE] and modified Stroop test [MST]). The MST was used to measure the ability to shift one's perceptual set to conform to changing demands and suppress a habitual response in favor of an unusual one. This test consists of two parts. In part 1, 24 colored dots are arranged at random, and in part 2, the color sequence is the same, but a different color name is written in Kanji (a Chinese character) instead of a colored dot. The Japanese version using colored Kanji (part 2) was created by Kashima.[11] The participants were requested to read out the color of the dot or Kanji as quickly as possible. The difference in time between the two parts was used to detect an inability to inhibit stereotypical behavior caused by frontal lobe dysfunction.

A brain MRI examination was performed with a 1.0-T superconducting magnet (Shimadzu, Magnex XP, Kyoto, Japan) using the spin-echo and the fast spin-echo techniques and fast fluid-attenuated inversion recovery sequences. Transverse T1-weighted (TR/TE = 510/12 milliseconds), T2-weighted (TR/TE = 4300/110 milliseconds), and fluid-attenuated inversion recovery (TR/TI/TE = 6744/1588/22 milliseconds) images were obtained with a slice thickness of 6 mm with a 1-mm interslice gap. Brain infarcts were shown as low signal intensities on T1-weighted images, and their size was 5 mm or larger. We recorded the quantity of brain infarction, the sites, and the lobes of the brain exhibiting abnormal MRI features. Sites were categorized as the corona radiata, basal ganglia, thalamus, and others, and the lobes of the brain with lesions were categorized as the frontal lobe, temporal lobe, parietal lobe, occipital lobe, basal ganglia, and others. Dilated Virchow-Robin spaces were differentiated from brain infarction based on reports by Takao et al[12] and Bokura et al.[13] The WMLs were defined as isointense with normal brain parenchyma on T1-weighted images, and high signal intensity areas on T2-weighted images. The MRI data were modified from 256 × 256 pixels to 512 × 512 pixels, and then were transferred from the MRI unit to a computer (Macintosh). The area of WMLs and brain volume were quantitatively measured using a semiautomatic method as previously described.[14] To correct for an individual difference in head size on the measurement of area of WMLs and brain volume, they were calculated as percentages of total intracranial area and volume, and defined as %WMLs and %Brain, respectively. All scans were reviewed independently by two authors (H. Y. and A. U.) who were blinded to all clinical data. In the case of disagreement between the raters, a consensus reading was held.

All values were given as mean ± SD. We used a software package (SPSS Advanced Statistics, Version 6.1, SPSS, Chicago, IL) for the statistical analysis. A univariate analysis was performed with a t test for continuous variables and the Chi-square test for categorical variables. We chose the variables for entry into the multivariate analysis based on the clinical and neuroradiologic findings with P values of less than .10 after univariate testing. Multivariate analysis was done using a logistic regression model to identify any factors indicative of the cognitive impairment defined by MMSE and MST. We used the forward stepwise method of the logistic analysis.

Results

The participants (121 male and 229 female) had a mean age of 72.4 ± 1.7 years and a mean educational level of 8.7

Table 1. *Clinical and neuroradiological features of subjects with or without cognitive impairment defined by MMSE*

	Cognitive impairment (+) (n = 55)	Cognitive impairment (−) (n = 295)	*P* value
Age (y)	76.8 ± 6.9	71.6 ± 6.6	<0.0001
Sex (M/F)	16/39	105/190	0.4375
Education (y)	7.5 ± 1.4	8.9 ± 1.7	<0.0001
Hypertension (+)	26 (47%)	102 (35%)	0.1012
Hyperlipidemia (+)	3 (5%)	44 (15%)	0.0942
Systolic blood pressure (mm Hg)	157 ± 29	143 ± 23	<0.0001
Diastolic blood pressure (mm Hg)	77 ± 11	77 ± 10	0.8148
Blood chemistry			
Packed cell volume	0.37 ± 0.04	0.39 ± 0.04	0.0002
Albumin (g/L)	42.7 ± 3.2	43.1 ± 2.6	0.3199
Fasting blood glucose (mmol/L)	5.31 ± 1.17	5.31 ± 1.17	0.9663
Total cholesterol (mmol/L)	5.04 ± 1.18	5.05 ± 0.85	0.9243
HDL cholesterol (mmol/L)	1.45 ± 0.30	1.52 ± 0.38	0.2053
Creatinine (μmol/L)	65.7 ± 17.0	62.1 ± 16.3	0.1364
Abnormal neurological signs (+)	4 (7%)	15 (5%)	0.7389
MRI findings			
% WML (%)	7.82 ± 4.73	4.70 ± 4.04	<0.0001
% Brain (%)	82.6 ± 5.4	86.5 ± 5.3	<0.0001
Brain infarction (+)	12 (22%)	44 (15%)	0.2794
No. of brain infarction per case	2.33 ± 1.37	1.86 ± 1.55	0.0937

Values are mean ± SD.
WML, white matter lesion.

± 1.7 years. Silent infarction was detected by MRI in 56 of the 350 volunteers (16.0%). The %WMLs ranged from 0.4% to 29.7% (5.2 ± 4.3%) of the intracranial area. The %Brain ranged from 67.6% to 96.5% (85.8 ± 5.5%) of the intracranial volume.

A total of 55 individuals (15.7%) with MMSE score less than 24 were operationally defined as having a cognitive impairment. They were older and had a lower educational level, lower hematocrit, larger WMLs, and more remarkable cerebral atrophy (Table 1). In a multivariate analysis, there was a significant relationship between cognitive impairment defined by MMSE and %WMLs, %Brain, and education (Table 2).

Frontal lobe dysfunction defined by MST score greater than 37 seconds was determined to be present in 52 participants: almost the same number of participants found to have cognitive impairment as defined by the MMSE. They were older and had a lower hematocrit, lower total cholesterol, significantly larger quantity of WMLs, more remarkable cerebral atrophy, and more brain infarcts (Table 3). In a multivariate analysis, impaired frontal lobe function was related to number of silent lacunar infarcts, larger WMLs, and more remarkable cerebral atrophy (Table 4). MST score of participants with two or more infarcts was significantly more prolonged compared with MST score of those without infarction (data not shown). Brain infarction existed predominantly in the middle cerebral arterial region. Multivariate analysis on the relation between the lobe with brain infarction and MST score after adjusting for age, sex, and educational level revealed an independent correlation between MST score and the frontal lobe brain infarction (odds ratio 3.10, 95% confidence interval 1.10-8.79). An independent correlation was also established between MST score and corona radiata brain infarction (odds ratio 2.97, 95% confidence interval 1.07-8.29). There was no difference in MST and MMSE concerning the laterality of hemisphere (data not shown).

Discussion

These results suggest that WMLs may cause rather generalized cognitive decline, whereas multiple lacunar infarcts are more specifically related with frontal lobe dysfunction. With subcortical lesions or small-vessel disease of this kind, the mechanism that impairs cognitive function is fundamentally the same as the mechanism of dementia in subcortical ischemic vascular dementia or vascular dementia of the Binswanger type (i.e., diaschisis).[15] In this study, of course, relatively minor cognitive impairments were revealed in the sample of community-dwelling nondemented people.

We studied a relatively large sample of community-dwelling individuals, using quantitative semiautomated methods of MRI analysis. The substantial contribution of silent ischemic lesions would be missed without inclusion of MRI, and the significant relation between WMLs or brain atrophy and cognitive dysfunction could not have been detected without quantification data. There are several limitations to this study such as the narrow

Table 2. *Logistic regression analysis of factors affecting cognitive impairment defined by MMSE*

Variables	β	SE	*P* value	OR	95% CI
% WML (/5%)	0.0989	0.0332	0.0029	1.640	1.184-2.270
% Brain (/5%)	−0.0763	0.0303	0.0117	0.683	0.508-0.919
Education (/y)	−0.5407	0.1342	0.0001	0.582	0.448-0.758

β, coefficient; SE, standard error; OR, odds ratio; CI, confidence interval.

scope of the cognitive assessment and cross-sectional nature. In the current study, we used exclusively the MMSE and MST for evaluation, although many kinds of assessment can be applied, as has been done in the Framingham Study.[16] The use of a broader test would have produced a more in-depth evaluation of the neuropsychological characteristics of VCI in the general population. In particular, loss of motivation or apathy frequently mimics frontal lobe dysfunction and should be evaluated by other means such as apathy scale[17] in future studies. Longitudinal studies should clarify whether the VCIND group develops vascular dementia or mixed dementia.

Several studies[18-20] have found a pattern of frontal lobe dysfunction in patients with multiple lacunes including difficulty in shifting set, impaired executive functions, decreased verbal fluency, and apathy. Looi and Sachdev[21] conducted a meta-analysis and found that disturbance in verbal memory as a neuropsychological characteristic of vascular dementia is less prominent compared with Alzheimer's disease, but there was significant impairment of executive function, which is considered to be the result of impairment of the frontal lobe-subcortical circuit. As mentioned above, the localization of the infarction is more important than its volume, and the frontal deep white matter can be postulated to exert a crucial role in frontal lobe function consistent with the results of our study.

Even if it does not develop dementia, silent infarction commonly seen in community-dwelling people has apparent detrimental effects on cognitive function, and additional silent infarcts after baseline further impairs cognition.[22] There are, however, various opinions as to whether silent infarction progresses to vascular dementia. One of those opinions as found in the nun study[23] is that dementia caused exclusively by brain infarction (here referring to mainly asymptomatic lacunar infarction) is not common. But when brain infarction merges with Alzheimer's disease pathology, it becomes apparent as

Table 3. *Clinical and neuroradiological features of subjects with or without cognitive impairment defined by MST*

	Cognitive impairment (+) (n = 52)	Cognitive impairment (−) (n = 298)	*P* value
Age (y)	77.2 ± 7.6	71.6 ± 6.5	<0.0001
Sex (M/F)	22/30	99/199	0.2656
Education (y)	8.5 ± 1.9	8.7 ± 1.7	0.5086
Hypertension (+)	24 (46%)	104 (35%)	0.1628
Hyperlipidemia (+)	3 (6%)	44 (15%)	0.1247
Systolic blood pressure (mm Hg)	151 ± 25	144 ± 24	0.0772
Diastolic blood pressure (mm Hg)	76 ± 10	77 ± 10	0.6449
Blood chemistry			
Packed cell volume	0.38 ± 0.04	0.39 ± 0.04	0.0122
Albumin (g/L)	42.4 ± 3.3	43.1 ± 2.6	0.0503
Fasting blood glucose (mmol/L)	5.10 ± 0.59	5.35 ± 1.24	0.1643
Total cholesterol (mmol/L)	4.79 ± 1.00	5.09 ± 0.89	0.0275
HDL cholesterol (mmol/L)	1.54 ± 0.33	1.50 ± 0.38	0.5044
Creatinine (μmol/L)	66.4 ± 15.8	61.9 ± 16.4	0.0679
Abnormal neurological signs (+)	4 (8%)	15 (5%)	0.6533
MRI findings			
% WML (%)	7.67 ± 5.36	4.76 ± 3.94	<0.0001
% Brain (%)	81.8 ± 6.3	86.6 ± 5.0	<0.0001
Brain infarction (+)	16 (31%)	40 (13%)	0.0032
No. of brain infarction per case	2.25 ± 1.29	1.85 ± 1.59	0.0016

Values are mean ± SD.
WML, white matter lesion.