食事・栄養

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abstract

孤発性アルツハイマー病発症には遺伝因子以外に，栄養・運動などの生活習慣要因（ライフスタイル）が関連している．生活習慣のなかでは特に食事因子が重要で，抗酸化ビタミン不足，n-3系多価不飽和脂肪酸不足がアルツハイマー病の発症に関連する．また，エネルギーや脂質，糖の摂取過剰はインスリン抵抗性を引き起こし，アルツハイマー病の発症につながる．食事因子の改善のためにはサプリメントでなく食品から摂取することが重要である．アルツハイマー病患者に対し抗酸化ビタミン，n-3系多価不飽和脂肪酸の摂取を推奨し食行動全体の改善を目指す行動修正療法を行ったところ，30カ月間認知機能の低下を抑制することが可能であった．

I はじめに

アルツハイマー病（AD）は老人斑と神経原線維変化を特徴とする進行性の変性疾患である．ADのうち約5%は遺伝子異常によって家族性に発症するが，残りの大部分は孤発性であり，その発症にはApoE-ε4などの遺伝的素因に加えて食事や運動，休養などの生活習慣，精神的ストレスなどの関与が推定されている．また，ADにも高血圧，インスリン抵抗性，糖尿病，高脂血症など血管系の危険因子が存在し，脳血管性認知症との類似点が次第に明らかにされてきた．なかでも食習慣を中心としたライフスタイルの改善は可能であり，ADの予防として期待されている，本稿では，AD発症と食事・栄養，血管因子との関係，さらに栄養介入効果の実際についても述べる．

II ADの栄養学的問題点

ADと栄養の関連はこれまでの報告では次の三点に絞られてきている．第一に野菜・果物の摂取はアルツハイマー病を予防することで，ビタミンE，ビタミンCなどの抗酸化ビタミンやビタミンB群，葉酸の摂取によるADの予防は複数の前向き調査によって明らかにされている．第二は魚の摂取の予防効果で，魚油に含まれるドコサヘキサエン酸（DHA）やエイコサペンタエン酸（EPA）などのn-3系多価不飽和脂肪酸（PUFA）には抗炎症作用，抗血栓作用，脂質改善作用などがあり，魚を多く摂取すればそれだけADが予防されるとの疫学調査が多く出されている．第三は糖・エネルギー代謝に関連するものであり，総カロリーおよび脂質，糖の摂取過剰の問題および糖尿病，インスリン抵抗性，高インスリン血症との関連である．エネルギー摂取過剰や高脂肪食はフリーラジカルの増大，サイトカインによる炎症反応の促進などよりADを起こしやすくする．

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III AD患者の栄養調査

Sasakiらの開発した自記式食事暦法調査票（self-administered diet history questionnaire：DHQ）を用い，あらかじめ患者および介護者より同意を得たうえで，AD患者と健常対照者の食事栄養調査を行い比較検討した[1),2)]．表1はAD患者の摂取食品の特徴である．この調査はすでに認知症を発症している場合での横断的研究であり，厳密な意味では認知症と食事との因果関係を証明するものではないが，AD患者の若いころからの食習慣をかなりの程度抽出することが可能である．健常対照者に比べて魚，緑黄色野菜，淡色野菜，キノコ類，海藻の摂取量が少ないことが明らかにされた．栄養素ではビタミンB_{12}，ビタミンB_6，葉酸，ビタミンC，ビタミンE，カロテンなどの摂取が少なかった．高齢の一般住民でも認知機能が低下している群ではこれらの栄養素が低下していることがすでに報告されている[3),4)]．脂質ではコレステロールの摂取に差はなく魚に含まれるEPAやDHAなどのn-3系PUFAの摂取が少なく，肉や植物油に多く含まれるリノール酸やアラキドン酸などのn-6系PUFAの摂取が多く，その摂取バランスを示すn-6/n-3比が有意に高かった．

IV 野菜・果物の摂取不足

ADと抗酸化物を含む食品の予防効果に関心が寄せられ，多くの報告がある[5)]．ロッテルダムからの大規模な調査報告[6)]では抗酸化物をβカロテン，フラボノイド，ビタミンC，ビタミンEの4つに分けて検討している．調査は55歳以上の5,395人を平均6年追跡し，この期間中に197人が認知症となり，うち146人がADであった．栄養調査は食品摂取頻度調査にて行い，ビタミンC，ビタミンE，マルチビタミンなどのサプリメントの使用状況（種類と量），栄養指導の有無を加えた．抗酸化物の最大量摂取群は最小量摂取群に比して，ADに罹患する危険率はビタミンCの場合には0.66，ビタミンEの場合は0.57と有意に低かった．サプリメント使用者は最大量摂取群に含めたが，サプリメント使用者を除外しても結果は同じであった．また，シカゴのMorrisら[7)]の報告では1993年から2000年まで平均3.9年間追跡調査し，65歳以上の815人のうちこの期間に131人が認知症になった．抗酸化物を食品のみから摂取した場合と，食品とサプリメントの両者から摂取した場合に分け，摂取量を5分割して解析したところ，ビタミンEを食品のみから摂取した場合にのみ抑制効果が認められ，食品とサプリメントの両者から摂取した

		AD（n=64）	N（n=80）	P値
穀類	(g)	261.9 ± 105.8	231.9 ± 94.1	NS
魚	(〃)	40.5 ± 24.4	58.3 ± 28.2	0.0001
肉	(〃)	25.1 ± 15.4	21.0 ± 16.3	0.13
緑黄色野菜	(〃)	45.7 ± 31.7	68.9 ± 59.8	0.01
カルシウム	(mg)	301.7 ± 121.9	413.0 ± 154.5	<0.0001
リン	(〃)	545.4 ± 131.0	644.4 ± 159.4	0.0001
カリウム	(〃)	1229.9 ± 326.6	1541.6 ± 455.2	<0.0001
カロテン	(〃)	1034.1 ± 855.6	1536.8 ± 1130.5	0.004
ビタミンC	(〃)	65.1 ± 34.2	86.4 ± 37.7	0.001
ビタミンB_1	(〃)	0.5 ± 0.1	0.5 ± 0.1	NS
ビタミンB_2	(〃)	0.7 ± 0.2	0.9 ± 0.2	NS
ナイアシン	(〃)	7.5 ± 2.2	8.6 ± 2.5	NS
コレステロール	(mg)	147.4 ± 77.0	153.7 ± 67.0	NS
SFA	(g)	7.2 ± 2.1	7.4 ± 2.8	NS
MUFA	(〃)	8.8 ± 2.7	8.3 ± 2.7	NS
n-6 PUFA	(〃)	5.4 ± 1.5	5.0 ± 1.4	NS
n-3 PUFA	(〃)	1.3 ± 0.6	1.6 ± 0.6	0.017
n-6/n-3		4.3 ± 1.4	3.4 ± 1.0	<0.0001

表1
アルツハイマー病患者の摂取食品と栄養素
N：健常対照者
SFA：飽和脂肪酸
MUFA：一価不飽和脂肪酸
PUFA：多価不飽和脂肪酸

場合には抑制効果がなくなった．

これらの疫学調査が示すように，抗酸化物を含む野菜・果物の摂取は認知症予防に有効だが，サプリメントのみでなく食品として摂ることが重要である．また，野菜には葉酸が多く含まれるため高ホモシステイン血症の予防を通じてADの発症を少なくしていることも考えられる．

V 魚の摂取不足と魚油の役割

ロッテルダムの調査[8]では，認知症のない55歳以上の住民5,386人を2.1年間追跡したところ，総脂質と飽和脂肪酸の摂取過剰が血管障害を伴う認知症の危険因子であったが，純粋なADに関しては魚の摂取は防御因子であり，魚を1日3g以下しか摂取しない群に比して18.5g以上摂取した群は有意に危険率が低かった（オッズ比0.3）．

ボルドーの調査[9]では，68歳以上の認知機能の正常な高齢者1,674人のうち1,416人を7年間追跡し，この期間中に170人が認知症になり，そのうち135人はADであった．その結果魚を少なくとも1日1回摂取する場合を基準にすると，少なくとも週に1回食べる場合のAD発症の危険率は1.64，2週に1回では2.24，全く食べない場合は5.29であった．肉を少なくとも1日に1回食べる場合は1.75であったが，肉を全く食べないと6.23と高くなることより，やはり肉も必要であることを示している．

さらにシカゴの調査結果[10]でも同じだった．815人を平均3.9年追跡し，この間に131人がADに罹患したが魚を週に1回以上食べる群はそれ以下の群に比してAD発症の危険率は0.4であった．また，総n-3系PUFAの摂取量を5分割すると，最大量摂取群は最小量摂取群に比して危険率は0.4であった．心筋梗塞や脳梗塞の既往によって食事を肉食から魚食に変更した例を除くと，魚の防御効果はさらに明らかになった．

魚油に含まれるn-3系PUFAは抗炎症作用，抗不整脈作用，抗血小板凝集能亢進作用，抗動脈硬化作用を通じて心血管系に良好に作用する．また，魚と野菜の摂取は血清コレステロールと中性脂肪を下げ，HDLコレステロールを上げる．ADにも動脈硬化が関与するとの知見が増加してきているが，魚油はこの点でも有利に働くものと考えられる．また，ADには慢性炎症が関係するという仮説があり，予防や治療として非ステロイド系抗炎症剤（NSAIDs）の投与が試みられている[11]．NSAIDsはアラキドン酸由来のエイコサノイドを産生するシクロオキシゲナーゼ（COX1とCOX2）の作用を阻害するため，NSAIDsを服用することと魚油を摂取することは同等の作用をもつと考えられる．さらに最近の知見では，アミロイドβ蛋白を脳から消去し血液へ移行させるアミロイド結合蛋白として注目されている蛋白にトランスサイレチンがあるが，n-3系PUFAを多く含む餌を老齢ラットに与えると，海馬のトランスサイレチンの発現が10倍にも増加することが見出された[12]．一方，n-6系PUFAは肉や植物油に多く含まれ，n-3系PUFA由来とn-6系PUFA由来のエイコサノイド（プロスタグランジン，トロンボキサン，ロイコトリエン）の生物活性は互いに拮抗関係にあるためn-6系PUFA由来のエイコサノイドが多くなるほど炎症，動脈硬化，血栓形成に傾く．肉は良質なタンパク質源でビタミンB_{12}も豊富な食品のため大切であるが，摂取に際しては極端な偏りは避けバランスを保つこと，つまりn-6/n-3比を極端に上昇させないことが重要である．さらに最近ではアミロイド蛋白を蓄積させる遺伝子導入のマウスにDHAを大量に与えるとアミロイド蛋白が抑制されるとの実験結果も報告され[13]，神経細胞に対する直接的な影響も検討されてきている．このモデルでは神経細胞膜の物理化学的な流動性に与えるDHAの効果が推定されており，非常に興味深い．

VI エネルギー摂取過剰，肥満，糖尿病，インスリン抵抗性

最近，肥満がADの危険因子であることがスウェーデンの18年間の前向き調査で明らかにされた[14]．79～88歳でADになった群の70～79歳でのBMIは28.2～29.6であり，認知症にならなかった群の25.0～25.7に比して有意に高かった．この結果は女性にだけあてはまり，男性では患者数が少なく有意差はなかった．一方Honolulu-Asia Aging Studyでは1,890人の男性について32年間の前向き調査を行った結

果，後半6年間の体重減少率は認知症を発症した男性が0.36kg/年で発症しなかった男性の0.22kg/年より多かった[15]．われわれの調査ではBMI25以上を示すAD患者は正常対照者の34.6%（19/55）に比して18.3%（20/109）と少なく，認知機能とは必ずしも関連が認められなかった．日本人は，欧米人とは異なり肥満者が少ないため発症前の一定期間での体重変化を加味した検討が必要である．しかし，自験例ではエネルギー摂取過剰例がほとんど（94.5%）であり肥満にならないまでも，エネルギー摂取過剰はAD発症と大いに関連がある．また，われわれの調査ではAD患者では糖尿病の割合は健常対照者とほぼ同じであったが，空腹時のインスリン値が高く，インスリン抵抗性を示す報告が多かった．さらに耐糖能障害のないAD患者では高インスリン血症が72.7%（32/44）と正常対照者より有意に高率であった（$p=0.03$）．規則的な運動がADを予防するとされているが，運動するほどインスリン感受性が高くなり，空腹時のインスリン値が低下することと関連している可能性がある．Craftら[16]の報告では，ADでは髄液のインスリン値が対照よりも低く，インスリンの髄液/血清比は有意に低い．さらに，Watsonら[17]はインスリンを点滴すると髄液中のアミロイドβ蛋白（Aβ42）が一過性に増加することを示し，この傾向は特に高齢者に著しいとしている．さらに，海馬のCA1およびCA3領域にはインスリン受容体の密度が高いことより記憶との関連に興味が持たれている．最近，インスリン分解酵素（insulin degrading ewnzyme：IDE）がAβ蛋白をも基質とすることが明らかにされ[18]，しかも，IDEはAβ蛋白よりもインスリンの方にはるかに親和性が高いため，高インスリン血症があると，相対的にAβ蛋白の分解が抑制されるという．高インスリン血症は血管内皮細胞の機能障害を起こすことが知られているため，インスリン自体が脳最小動脈の内皮細胞障害を起こしている可能性がある．

Ⅶ AD患者への栄養学的介入

AD患者に対して食事による治療への応用はまだほとんど行われていない．AD患者の栄養調査結果をもとに患者および介護者より同意を得たうえで，われわれは食行動全体の改善を目指す行動修正療法を試みている．魚を1日1回，緑黄色野菜1日2回，果物を1日1回摂取することを推奨している．この食事で栄養素を計算すると，ビタミンやミネラルの必要量を満たし，n-6/n-3比は3.0程度となる．このような介入を行った群のうち栄養指導をよく守った群（遵守群）はよく守らなかった群（非遵守群）と比較すると，全AD患者でミニメンタルテスト（MMSE）の変化が30カ月の段階で平均5.2点高かった（図1）．また非介入群でのMMSEの変化は非遵守群と酷似しており，栄養指導をよく受け入れることが認知機能の維持あるいは改善に直結することが明らかとなった．栄養介入は介護者の協力なくしては成り立たないため，患者とともに食事担当者や同居者で食事

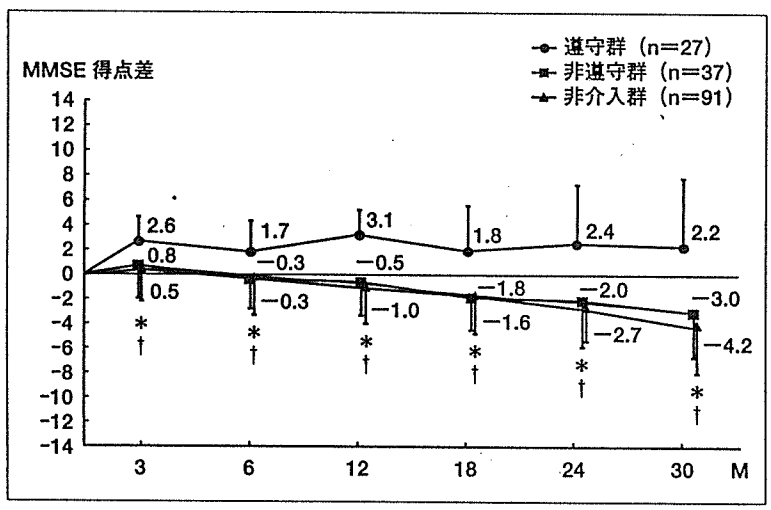

図1
アルツハイマー病患者の栄養介入によるMMSE得点差—全体—
*：$p<0.05$：遵守群 vs. 非介入群
†：$p<0.05$：遵守群 vs. 非遵守群

摂取状況の把握が可能な観察者が栄養士から食行動の問題点に応じた指導を受けることが重要である.

VIII まとめ

ADの発症には遺伝的素因が大きい患者がいることも事実であり食事だけではすべてを説明できないことも明らかである. ADの本質にはインスリン抵抗性と, その背景にある高エネルギー, 高脂質を摂る食行動が関連している可能性があり, 食事栄養の意味づけがより明確となりつつある.

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Review Article

Alcoholic Brain Damage and Dementia viewed by MRI; with Special Consideration on Frontal Atrophy and White Matter Damage in Dyslipidemic Patients

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Abstract

Long-term intake of excessive alcohol causes a variety of brain damages, most of which are now visualized by MRI and proved to be contributing to the early onset of dementia. Bi-frontal atrophy takes a unique position among those various damages because of its lobar conformation localized only to higher cortex, and because the same kind of atrophy is also seen in dyslipidemic patients like hypercholesterolemia. Multiple logistic regression analysis of 3100 subjects with MRI revealed no other significant group with this finding. Morphological features of this type of atrophy and its rate of progression are described, and computerized image analysis showed this atrophy seems to depend mainly on the decrease of white matter. However, a common biochemical factor underlying the frontal atrophy of these tow groups is not yet identified. Importantly, dyslipidemic patients also show some types of T2 high white matter changes, which are not seen in pure alcoholics. For dyslipidemic patients, this white matter change, which seems to be a degradation of myelin sheath, is another basis for early dementia. Though the author can propose a new concept of 'dyslipidemic dementia' due to frontal atrophy and white matter damage, details of mechanism and its relation to alcoholism are left to the future investigation.

Key words; alcoholics, frontal atrophy, hypercholesterolemia, white matter, dementia, T2 high intensity spots, dyslipidemia

Introduction;

It has been well known from the ancient times that the excessive

alcohol intake for a long period of time causes various types of physical, cerebral, and psychic damages. Table1 shows well-documented damages and diseases of central nervous system (CNS) seen in heavy drinkers (1). It is noticeable that most of them are only indirectly related to ethanol itself. Vitamin deficiency, drastic change of osmotic pressure, hypoglycemia, ...etc. All of them are not specific to alcoholism. However, their serious outcomes should be considered as definite alcohol-associated damages because they are not caused if the subject did not consume excessive alcohol. Dementia by a car accident of a drunken driver, dementia by hypertensive cerebrovascular accidents in heavy drinkers, dementia of alcoholics with severe frontal atrophy, are the other examples that should be included in the alcohol-related dementia problem. Our clinical standpoint necessitates that we should recognize all of the disorders listed in Table 1 as serious mechanisms of brain damage rooted in the excessive intake of alcohol.

Ethanol per se is rapidly metabolized after intake, but secondary metabolites like aldehydes and the other complex processes including enzyme inhibitions in sugar and fat metabolism, and neurotransmitter change like dopamine polymerization are believed to disrupt the human homeostatic system in CNS and lead to various disorders, e.g. some vitamin deficiency diseases, hypertension, cancers and atrophic changes of the brain. Recent development of magnetic resonance imaging (MRI) techniques succeeded to visualize the majority of these brain damages in their early stage (1). And it demonstrated that most of those pernicious changes start in younger days long before the appearance of clinical symptoms, and that they don't depend on whether the subject is 'dependent' on alcohol or not, and the mode of damage does not differ significantly by the species of liquors. Briefly to say, alcohol 'dependency' is another problem than those coarse physical damages in organs and brains. The first importance seems to be the total amount of ethanol digested through life, and abstinence seems to stop the most part of further progression of those disorders (2). Readers should refer to special articles for each item listed in Table 1. Here we focus on the more recent issues about alcoholic brain damage.

In the first part of this paper, the author deals with the problem of brain atrophy and intend to show an important linkage of alcoholic bi-frontal atrophy to the same finding seen in hyper- or dyslipidemic patients (3). This is of particular importance because alcoholism is famous for its strong interference with fat metabolism. The second part discusses the white matter changes in dyslipidemic patients, which is also important because this is the key issue to the white matter problem in dementia and partly explains why obese hyperlipidemic subjects tend to be demented earlier than the others.

1. Frontal atrophy in alcoholics and dyslipidemics;

Fig1 shows T2 weighted MR images of a typical frontal atrophy seen in a severe alcoholic of 45 years old. The atrophy is bifrontal and symmetrical (Fig1-a). In the horizontal plane, it starts from the first (upper) frontal gyrus and proceeds to the posterior part, and further over the Sylvian fissure in the advanced case. In the saggital section, the atrophy clearly develops most severely in frontal pole and tapers to the upper part, almost disappears before transverse gyrus except in severe cases. Very interesting is that the atrophy almost does not occur in the inferior surface of the frontal lobe (Fig1-b), which is phylogenetically older than convexity. Clinical features might be different if frontal base is involved. Fig2 is another example of the more advanced case of higher age. The atrophy apparently involves the inter-hemispheric surface of frontal lobe including cingulate gyrus, and also seems to suspend at the transverse gyrus in the convexity (Fig2-b). Frontal atrophy with these features is quite common in heavy drinkers, and frequency increases almost lineally by age among those with daily intake of more than 90-gram ethanol for many years (Fig3). When the extent of atrophy is classified into three grades (FA1; mild, FA2; moderate, FA3; severe), moderate to severe cases also increases with age. Fig. 1 and Fig. 2 are, of course, severe cases.

The important question is whether this type of frontal atrophy is specific to alcoholism or not. Before dealing with this issue, we have to settle a couple of the other misleading topics. First, when X-ray CT

began to be used to visualize brain atrophy in late 1970's and early 1980's, recovery was believed to be common to alcoholic brain atrophy (4). However these studies did not differentiate lobar atrophy from diffuse type (5). Diffuse type of brain 'shrinkage' as observed often in the case of severe anorexia nervosa or starved alcoholics and other malnutrient conditions actually recover after adequate supply of water and other nutrients. But, lobar atrophy as shown Fig.1~2 does not recover (2). They are different phenomena. Although more than a thousand of cases were followed in these eighteen years with MRI, not a case showed even a partial recovery. Cerebral lobes tend to be atrophic in higher age, nevertheless frontal atrophy is unquestionably discernible by its unique features even at the age of 80's as shown in Fig.2. Secondly, an old and simple question was sometimes repeated about the position of the head and the effect of gravity during the MRI examination, i.e. the atrophied brain could be 'sinked' downward if the face looked upward. But the inferior surface of the brain is adequately 'socketed' into the several bone cavities and finely connected by membranes and fibers to the skull. One can easily confirm this by the experiment in which a subject looks downward during the examination.

Very interestingly, the frontal atrophy seen in alcoholics is not specific, because we found the same type of atrophy in another large patient group with hypercholesterolemia (i.e. total serum cholesterol level >= 220mg/dl). The same type of bilateral frontal atrophy is quite common in the hypercholesterolemic and/or hypo-HDL (high density lipoprotein) group (Fig4). The latter group is defined by higher arteriosclerotic index and relatively high serum cholesterol (>=200mg/dl). The frequency of frontal atrophy among this second group seems to be lower and the age is higher if compared with the severe alcoholics. However, this group is very important because the total number of dyslipidemia is huge in general population, and indiscernible progress of atrophy slowly leads to the hypo function of frontal lobe and finally to dementia (Fig5). Mild frontal atrophy usually does not draw clinical attention, however, anxiety, mild

depression, and insomnia is fairly common in over-middle age females with this MRI finding. Our statistical analysis showed significant correlation between depressive syndrome and hypercholesterolemia, and frontal atrophy is sometimes suggested as a cause. Even moderate degree of frontal atrophy is also associated with psychic symptoms and sometimes shows abnormal scores in dementia scale. Many cases with severe frontal atrophy have impaired cognitive function of frontal type and often suspected to have Alzheimer's disease. On the other hand, the frontal type of Pick's disease is rarely suggested because clinical features are too different.

Multiple logistic regression analysis of 1300 middle to high aged subjects showed no other significant factors for this type of frontal atrophy (6). Relative risk of long-term alcoholism (>90 grams/day) for frontal atrophy is 5.4 ($p<0.0001$) in males, and 6.4 in females. Alcoholism is also significant for temporal atrophy (relative risk 2.4, $p<0.0002$) and dilatation of lateral ventricle (2.7, $p<0.001$) especially in higher ages. Of course these figures include various aspects of risk factors and do not represent the exclusive effect of alcohol itself. On the converse, the relative risk value of frontal atrophy for dementia calculated by the same patient series (3000 subjects) is 2.1($p<0.001$). This is not particularly high among various MRI findings, because the relative risk of temporal lobe atrophy for dementia is 2.2($p<0.001$), and 1.9 in periventricular T2 hyperintensity ($p<0.01$)(7). But these figures are not decisive but dependent on models we employed and also on the grading method of various MRI findings. The next discussion is on the biochemical mechanism of frontal atrophy of these two groups.

2. Mechanism of frontal atrophy in alcoholics and dyslipidemics

The frontal atrophy observed in MRI is so typical that the long ignorance shown by researchers and clinicians seems to be strange. Still many doctors think it is a natural phenomenon that the brain 'shrinks' according to the age. This is partly true and partly wrong. There are many healthy 70's who show virtually no signs of cortical atrophy, especially in frontal lobe. But in the outpatient clinics most

elderly patients show more or less abnormal signs including some type of cerebral atrophy and/or ischemic changes. Relative risk of hypertension for T2 high intensity spots in basal ganglia and in deep white matter is 2.4($p<0.0001$) in both cases (8). However, many clinicians tend to believe findings seen in the major portion of patients are 'normal' or 'natural'. That's why hypercholesterolemia also didn't draw attention as a cause of hypo-cognition for such a long time, and this attitude partly explains the reason of ignorance on the meaning of frontal atrophy. Relative risk of hypercholesterolemia for frontal atrophy is as high as 2.2 for females ($p<0.002$)(6). But there is another reason, which is more serious and academic. Researchers on alcoholic brain damage have tried to find the neuropathological basis of atrophy for a long time by various methods (9). However, as far as the light microscopic study is concerned, neurons did not seem to degenerate and disappear as in the case of the other degenerative disorders, and white matter did not show any typical demyelinative changes. Of course clinical experience tells that the severe frontal atrophy as shown in Fig.1~3 is associated with lowered cognitive function, or at least mild dementia in most cases. So the cause of alcoholic brain atrophy and dementia has been left as a kind of paradox (10, 11).

So far, MRI did not solve this paradox completely. But our computerized image analysis showed the volume of white matter tends to be decreased more clearly than the gray matter (Fig6)(12). There was no important difference in this result between alcoholic and hyperlipidemic groups. If this is true, frontal atrophy in alcoholics largely depends on the decrease of white matter, which probably means myelin sheath looses its volume by some or the other metabolic derangements. And well-documented ventricular dilatation in alcoholics also seems to be explained by this decrease (13). Although sphingomyelin and other important lipids constituting the sheath of neuronal fibers and membranes have been believed to be synthesized de novo in the CNS and not affected by the serum lipid level, the fact that hyperlipidemia is strongly associated with the frontal atrophy may indicate that the old belief to be reconsidered. There are some

reports indicating serum high lipids could cause some change in neurons and glias (14,15), and the correction of clinical hyperlipidemia recovered cognitive dysfunction (16,17). Lipid metabolism within CNS seems to be different from other organs (18). This 'white matter hypothesis' of frontal atrophy seems to be reasonable, because if the neuronal cell loss is the main cause of frontal atrophy, cognitive dysfunctions should be more severe from the early stage both in alcoholism and dyslipidemia. Though this doesn't deny that neurons decrease their size and loose a part of their functions, at least microscopic examination of alcoholic brain did not demonstrate the plain neuronal losses in frontal cortex so far. There are some reports on the change of dendrites in alcoholic brain, but not fully reconfirmed (19). More sophisticated analysis of neuropathological study suggested that the loss of volume in alcoholic brain mainly came from the decrease of white matter, particularly in prefrontal lobe (20). Selective neuronal cell loss was also found in superior frontal cortex. These findings could be consistent with our "white matter hypothesis". If so, further study of hypercholesterolemic frontal atrophy with the same method should also be needed.

Progression of the frontal atrophy is very slow. According to our image analysis, the rate of progress is 0.3~0.7 % per year of the prefrontal brain defined as an area in front of the anterior horn in the horizontal section, although that is sometimes around 1 % per year in extreme alcoholics. Alcohol almost freely passes blood brain barrier (BBB) and easily interferes with the lipid metabolism, which seems to give the basis for white matter change. However, little is known about the specific basis for frontal lobe vulnerability to those risk factors and the knowledge on the changes of lymphokines including growth factors in CNS of alcoholism and dyslipidemia is scarce. We have to wait until the recent development of neuronal (stem cell) culture and related biochemistry throw new light on this old issue.

3. Relation to T2 high changes of the white matter in dyslipidemics

T2 high intensity spots and maculae are quite common in the

white matter of hyperlipidemic patients (Fig7), but the meaning of these MRI findings has not been properly recognized. In most cases they are interpreted as a sign of ischemic tissue damage due to the hypertensive and/or hypercholesterolemic vascular occlusion in small arteries (21). However, hypertensive small vascular damage has been well known to occur primarily in the perforant arterioles of basal ganglia area. They are easily recognized as small circular spots in the horizontal section, while T2 high spots and maculae in hyperlipidemic patients tend to appear in the periphery of white matter i.e. just below the cortex without significant change in basal ganglia and external capsule, and frequently merge to form a larger area. More typical T2 high foci in white matter of hyper- or dyslipidemic patients tend to occur above and along the dorsal surface of lateral ventricle (Fig7,8). They are different from so-called periventricular hyperintensity (PVH) in that the former usually doesn't merge to the upper lateral corner of the lateral ventricle probably because they are not formed by the destruction of vessels connecting to the ventricular corner. Those T2 high areas rarely show apparent infarction mode in MRI, i.e. the definite T1 low intensity comparable to water. A slightly decreased intensity is frequently observed in the identical locus of T1 weighted images in a patient with advanced T2 high areas in white matter, which probably means the loss of lipid component from the tissue.

The problem we ask here is, whether these white matter changes seen in dyslipidemic patients are also observed in alcoholics. The answer is no. Pure alcoholism without hypercholesterolemia does not show these findings. The multivariate analyses on the relationship between these two phenomena also revealed insignificant results (7, 8). Namely, alcoholism and its assumed derangements in lipid metabolism in CNS are not sufficient to form these findings in the white matter. As is well known, alcoholism usually decreases total serum cholesterol and increases HDL-cholesterol and triglycerides. Therefore, increased serum total or LDL-cholesterol is not necessary for frontal lobe atrophy and increased HDL-cholesterol has no relation to the T2 high white matter change. So far in peripheral blood, there seems to be no single

component common to the frontal atrophy in alcoholism and dyslipidemia. We seem to meet another paradox here again. A high level of triglycerides may play an important role, but high instability of their serum value hinders to settle this point because we cannot obtain an average value of long period of years or decades.

Another possibility is fatty acids and their imbalance. We examined the serum and intra-membrane fatty acids in red blood cell and their relation to those MRI findings. Results showed lowered EPA (eicosapentaensanic acid) and N6/N3 ratio has a significant positive relation with white matter change described above and dilatation of lateral ventricle, but their significance in frontal atrophy was not proved (22). Therefore, the T2 high white matter changes seem to be associated to the changes of several lipid components and their imbalance, but for the frontal atrophy we still cannot identify the crucial chemical factors.

Cerebral atrophy usually does not accompany T2 high change in the white matter, and the alcoholic frontal atrophy is not an exception. The fact it doesn't show any apparent change in MRI intensity means it probably is a simple shrinkage and doesn't have tissue or membrane destruction. This atrophy literally seems to be a trophic problem, which might be related to the change of trophic factors mainly effecting on the oligodendroglial cells. But the factor is unknown yet.

4. Conclusion

There are so many factors and mechanisms connecting excessive alcohol intake to brain damage, which in total make alcoholics demented much earlier than nonalcoholics. Among those, frontal atrophy is outstanding in its morphological, pathophysiological uniqueness and the relation to dyslipidemia, and is also important in its socio-psychological implication. Though the precise biochemical basis is not clarified yet, this atrophy seems to be associated with the derangements in lipid metabolism and white matter composition. Dyslipidemia including hypercholesterolemia should also be recognized as a cause of early dementia by its high frequency of frontal atrophy and white matter decomposition. Many discrepancies in our

present knowledge on the relation between alcoholism and dyslipidemia, frontal atrophy and white matter damage in MRI, should be solved by the further investigation.

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Legends

Table 1 Organic brain damages seen in heavy drinkers

Fig 1 T2 weighted images of frontal atrophy of alcoholism

A 45 y.o. male alcoholic patient with a history over 25 years showed typical frontal atrophy without other finding like lacunae. Atrophy seems to be most severe in frontal pole. (a); horizontal section, (b); saggital section through right eyeball

Fig 2 T1 weighted images frontal trophy in an elderly alcoholic

An 81 y.o. heavy drinker with dementia continued to drink more than 60 grams of daily alcohol even after his 70's. Atrophy involved a

part of temporal and parietal lobe, but occipital area is fairly well preserved. (a); horizontal section through anterior horn of lateral ventricle, (b); horizontal section through upper part of centrum semiovale.

Fig 3 Age-dependent frequency of bilateral symmetrical atrophy of frontal cortex among alcoholics

Among 405 alcoholics (91% are males) 231 cases (57%) showed slight to severe frontal atrophy. Age-dependency is clear. FA1; slight, FA2; moderate, FA3; severe

Fig 4 Age-dependent frequency of bilateral symmetrical atrophy of frontal cortex among hypercholesterolemic patients

Among 482 hypercholesterolemics, 197 (41%) cases showed frontal atrophy. Age-dependency is clear from 40's, but moderate to severe cases begin to appear from 50's.

Fig 5 A typical frontal atrophy of a hyperlipidemic patient

A 70 y.o. hyperlipidemic male without any other disease showed this type of bi-frontal atrophy. The patient showed moderate hypo-function in his cognition. The basic feature doesn't seem to be different from those in Fig 1.

Fig 6 Change of white and gray matter volumes according to the progress of frontal atrophy

A computerized image analysis of 42 cases with typical frontal atrophy showed gradual decrease of white matter percentage and increase of cerebrospinal fluid according to the atrophic grade. The volume of gray matter seems to be fairly stable. Results are calculated using horizontal sections with prefrontal intracranial volume as 100%. A statistical test by ANOVA showed significant difference in the decrease of white matter and compensating increase of cerebrospinal fluid. The grade of atrophy is shown by FA0: normal, FA1: mild, FA2: moderate, FA3: severe, FA4: extreme. ○; white matter, ●; gray matter, □; cerebrospinal fluid

Fig 7 Typical T2 high intensity spots in a hypercholesterolemic subject

A hypercholesterolemic female showed many T2 high intensity spots in

subcortical white matter, and middle-sized macula is seen adjacent to the posterior horn of lateral ventricle. The left (a) was taken at the age of 60, the right (b) 70 y.o. Though the slice position is slightly higher for A, eleven years seems to cause relatively small change probably due to the treatment with statin and control of fatty foods.

Fig 8 Saggital sections of a hypercholesterolemic subject

A 62 y.o. hypercholesterolemic female showed T2 high spots and macula in the left (a), eleven years of treatment seems to prevent apparent advance of the foci (b; right).

Table 1

Table 1 Organic brain damages seen in heavy drinkers

A. Atrophic change
1. frontal atrophy 2. temporal atrophy 3. sulcus dilatation.
4. dilatation of lateral ventricle 5. dilatation of 3 rd ventricle
6. atrophy of cerebellum and vermis 7. atrophy of mamillar body

B. Vascular damage
1. infarction, lacunae and bleeding mainly due to hypertension
2. so-called leukoaraiosis mainly due to hypertension
3. T2 hi intensity spots and maculae mainly due to dyslipidemia
4. periventricular hyperintensity (PVH)

C. Vitamin deficiency
1. Wernicke's and/or Korsakoff's syndrome mainly due to thiamin deficiency
2. Pellagra encephalopathy mainly due to nicotinic acid deficiency
3. Marchiafava-Bignami syndrome (?)

D. Traumatic damage
1. cerebral contusion and hemorrhage 2. subacute hematoma
3. chronic subdural effusion 4. diffuse axonal injury

E. Osmotic change
1. central pontine myelinolysis 2. extra-pontine myelinolysis

F. Others
1. hypoglycemic coma 2. carbon-monoxide poisoning
3. fetal alcohol syndrome 4. severe hepato-cerebral syndrome

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ドコサヘキサエン酸による脳機能改善作用と神経疾患への応用

Improvement Effect of Docosahexaenoic Acid on Neurological Function and Its Application to Neurological Disorders

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論文要旨：ドコサヘキサエン酸（DHA, 22：6n-3）は神経細胞膜リン脂質の構築成分であるn-3系必須不飽和脂肪酸であり，正常な脳の発達や視力を維持するのに極めて重要である。脳内のDHAが欠乏すると，神経伝達系，膜結合型酵素やイオンチャネル等の活性，遺伝子発現，およびシナプスの可塑性，等に著明に影響を及ぼし，そのためにDHA欠乏は，加齢に伴う脳機能異常，アルツハイマー病，うつ病，ならびにペルオキシソーム病などを誘発する。また，DHAの摂取不足は認知・学習機能を低下させるが，DHA摂取によりこの機能は回復するようである。疫学的研究によると，魚の消費が少ないとアルツハイマー病の罹患率が高いことから，魚油，とくにその主成分であるDHAによる神経保護作用が推察される。脳機能障害に作用するDHAの分子メカニズムは不明であるが，DHAを摂取すると，動物の学習機能障害が改善し，またアルツハイマー病モデルラットやマウスでの学習機能障害が予防，さらには改善される。本論文では，食餌性DHAによる記憶・学習機能向上効果，さらには臨床応用として脳機能障害の代表的疾患であるアルツハイマー病やうつ病との関連性について紹介する。

Abstract: Docosahexaenoic acid (DHA, 22 : 6n-3), an essential n-3 polyunsaturated fatty acid, is one of the integral components of neural membrane phospholipids and is essential for normal neurological development and vision. DHA deficiency markedly affects neurotransmission, activities of membrane-bound enzymes and ion channel, gene expression and synaptic plasticity; it is thus associated with some neurological dysfunction in aging, Alzheimer's disease (AD), depression and peroxisomal disorders. Deficiency in dietary DHA induces loss of discriminative learning ability; thus intake of DHA may restore this loss. Epidemiological studies show a relation between the ingestion of fish oils and AD, suggesting neuroprotective consequences of the oil, especially of DHA. Although the molecular mechanism of DHA involvement in neurological disorders remains unknown, dietary administration of DHA improves lost learning ability in animals, and protects against and ameliorates the impairment of learning ability in AD model rats and mice. The improvement effect of dietary DHA on memory/learning ability and its application to AD and depression in neurological dysfunction is reviewed here.

Key words: Docosahexaenoic Acid, Antioxidant, Memory and Learning, Alzheimer's Disease, Neurological Function

1　はじめに

長寿で健全な高齢化社会を構築するために，我々が克服しなければならない疾患の一つに老人性認知症があ

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