失行など巣症状や神経症状を伴う．③攻撃性，徘徊，幻覚・妄想などが認知障害以上に目立つ．こうした症状が介護者の負担感の主因とされるだけに，家族介護者の辛さは想像に難くない[4]．

(3)神経心理学的特徴

かつてアメリカではConsortium to Establish a Registry for Alzheimer's Disease（CERAD）という大規模な研究組織があった．この研究の一環として，早発性（65歳未満発症：98名）と晩発性（65歳以上発症：323名）のAD患者との間で，性，教育歴，認知症のステージを制御した上で神経心理学的所見が比較された．その結果，早発例では言語機能と集中力は不良だったが，記憶と見当識は優れていたとされる．そして全てのテストの成績について4年の追跡期間における低下率が有意に大きかったと述べられている[13]．

(4)画像所見，病理学的特徴

MRI画像所見からは，高齢発症例に比べて若年発症例では側頭・頭頂葉移行部における萎縮が有意に強いが，海馬の萎縮は弱いとされる[6]．PETやSPECTを用いた研究でも同様の指摘がなされている[12]．

一般に若年発症AD例では脳の萎縮はびまん性かつ高度であるのに対して，高齢発症例では側頭葉内側部に限局しがちである．また老人斑と神経原線維の出現量については，若年例の前頭葉や頭頂葉では生理的上限の10倍もみられるものの，生理的にも出現しやすい側頭葉では2～3倍程度にとどまる．またMeynert基底核や青斑核では神経原線維変化が生理的上限を超えて出現し，神経細胞の脱落も認める．これに対して高齢発症例では，全ての部位で増加率は1.5倍程度で一定している．

両者が病理学的に最も異なる点は，若年例ではアストログリアの反応など激しい変性が認められるのに，高齢発症例ではこれが乏しいことである．また前者では，6層からなる大脳皮質の構造が全層にわたって侵されるが，後者では部分的にとどまる点も重要である[10]．

2）前頭側頭型認知症（FTLD）

(1)疾患群概念の整理

ピック病をはじめとする大脳の前方部に主たる病巣をもつ変性性認知症は前方型認知症と通称される．前方型の多くを占めるものがFTD疾患群である．これは1994年にマンチェスター大学とルンド大学のグループ[21]からその特徴的な臨床所見と病理学所見をもとに提唱された概念である．

もっともこの用語や診断に関して混乱を生じた．そこで1996年にマンチェスター大学から前頭側頭葉変性症（fronto-temporal lobar degeneration: FTLD）という新概念が示された．この下にFTD，従来は側頭葉優位型ピック病とされた語義失語を主徴とする意味性認知症（semantic dementia:SD），そして進行性非流暢性失語（progressive nonfluent aphasia:PA）などが位置付けられた．

なおパーキンソン症候を伴う第17染色体17q21-22に関わる常染色体優性のFTDP-17，あるいは運動ニューロン疾患を伴う認知症，皮質基底核変性症の一部といった疾患単位もここに位置する[21]．

このようなFTLDと診断された353症例を検討した研究報告がなされている[11]．ここではFTD，SD，PAに3分類した上で検討された．その結果，平均発症年齢は，FTD 57.5歳，SD 59.3歳であり，PAの63.0歳より有意に早かった．またFTDとSDの2/3は男性であったが，PAでは男性は1/3強という性差も示されている．

一方病理学的分類としての，FTLDスペクトラムにおいて，最も多いのがピック球を欠くFTLD-lacking distinctive histology（ldh），次は20～25%程度を占めるFTLD-Pickである．さらに10%程度とされる運動ニューロン疾患を伴う認知症という下位分類もある[21]．今日言うところのFTDを，臨床家は伝統的にピック病と呼んできた．しかし多くのFTD症例ではピック病に特徴的とされる3リピートタウの凝集塊であるピック球を欠いている．そしてある種のFTDで

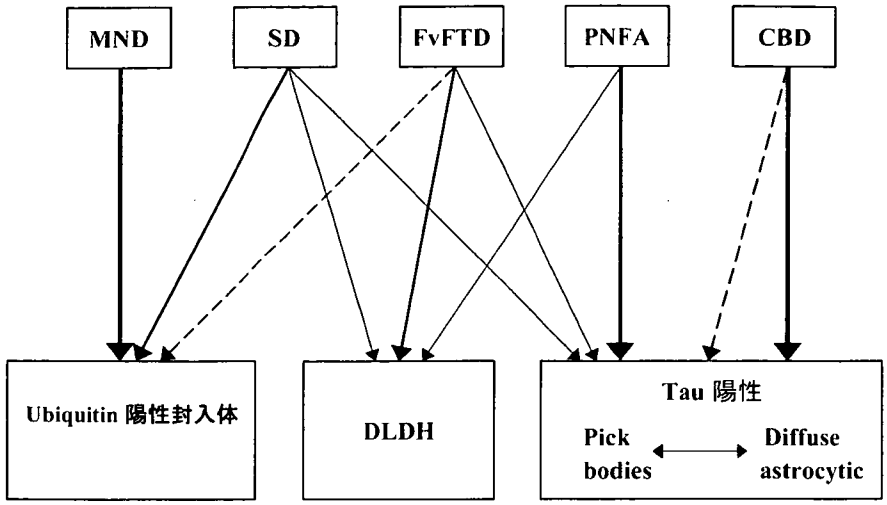

図　FTD とその関連疾患の臨床像と病理所見の対応
MND : motor neuron disease, SD : semantic dementia, FvFTD : frontal or behavioral variation of FTD, PNFA : progressive non-fluent aphasia, CBD : corticobasal-degeneration, DLDH : dementia lacking of distinctive histology
矢印の濃さは，臨床像と病理所見の対応関係の強さを示す．
〔Pick's disease. Dementia, 3rd ed. (ed. by Burns, A., O'Brien, J., et al.). Hodder Arnold, New York, p. 684 2005 を改変〕

は，FTLD-U とこれまでは呼ばれ，ピック球とは異なるタイプの封入体がみられる．これは体内に蓄積し不要となった蛋白質を除去する物質ユビキチンを含んでいる．このユビキチンがどんな蛋白質と結合しているのかに近年注目が集まっていた．これが TDP-43 という遺伝子発現を調整する蛋白質であることが明らかにされた[1,23]．

以上に述べた FTLD の臨床的な下位分類と病理学的なそれとは 1：1 に対応しない．このことが FTLD の全体像を複雑でわかり難いものにしている[21]．これを図に示したが，今後さらなる整理が待たれる．

ところで欧米の報告では，FTD の 40％は家族性であり，常染色体優性の遺伝様式を示す[8,33]．そしてタウ遺伝子との関係から第 17 染色体が注目されてきた．しかしタウ遺伝子異常によって説明し得る FTD は，孤発性はもとより家族性の例においても稀だとされる[33]．

一方，欧米とは異なり，わが国の例では家族例は少ない．筆者らは日本人 FTD の 24 症例においてタウ遺伝子の変異を検査した[14]．2 例の遺伝性 FTD 患者においてのみ異常を確認したが，孤発例では変異は全く認められなかった．

3) レビー小体型認知症（DLB）

DLB について近年診断基準の改定がなされ，いささか複雑化している．しかしその病理と臨床の基本が，以下の 3 点であることに変わりはない．①黒質線条体病変によるパーキンソニズム，②認知機能と神経精神医学徴候の基盤をなす皮質病変，③自律神経系の傷害である[18]．

DLB は AD と似てはいるが，多少とも異なった臨床症状，経過をとる．発症年齢は 50～83 歳と AD より若干低く，また死亡時の年齢は 68～92 歳とされる[19]．近年本疾患の有病率が予想以上に高いとして注目されるようになった．そして変性性認知症としては AD に次いで多いとも言われ，認知症全体に占める割合を 20％とした報告もある[26]．性差では，男性が女性の 1.5～2 倍程度多い[32]．

パーキンソン病に特徴的な病理所見であるレビー小体の主要成分はα-シヌクレインである．そこでDLBの遺伝子研究では，パーキンソン病との関係から第2，4染色体が注目されてきた．また注目すべきは，ADにおけるほどの影響力はないにせよ，APOE 4遺伝子が本疾患でも危険因子になるという事実である[25]．

多くの症例では，ADに特徴的な神経原線維変化と老人斑にDLBに特徴的なレビー小体が共存する．以前の国際ワークショップによれば，DLBと診断される剖検例の15％には重度の，55％にはある程度のAD病理がある．そして同年齢の対照と同程度のものは30％にすぎなかったとされる[17]．

なおDLB患者にみられる抗精神病薬への過敏性は有名である．ある回顧的調査によれば，このような現象がみられる危険性はADでは7％であるのに対して，DLBでは81％にも上ったとされる[16]．

V　わが国における当事者と家族の問題

当事者と家族が抱える問題点は以下の4点にまとめられる．すなわち，①医療とケア，②生活の経済的基盤，③家庭の不和，④子供への遺伝である．こうした諸問題についても具体的なことは，欧米でも[2]，またわが国でも殆ど知られていない．そこで筆者らは最近，奈良県の「朱雀の会」と東京の「彩星の会」という患者・家族会の会員の協力を得て表3に示す項目について調査した．105の有効回答をもとに結果概要を紹介する[2]．

1）受診・診断・告知

家族が何らかの異常に気付いた後に初めて医療機関にかかるまでの期間では，ときに3年以上という例もあるが，多くは1年以内であった．いわゆる老年認知症の場合には2〜3年とも言われるので，若年性の場合は相当速やかと思われる．とくにサラリーマンの場合，僅かなミスでも重なると会社側から受診を促されることもある．逆に3年以上も受診していないケースでは自営者が多いように思われた．

初めて受診した病院としては，総合病院が大多数を占める．診療科としては，精神科，神経内科，脳外科が多い．また認知症を告知された機関についても同様である．

なお総合病院といっても，実は調査地域における認知症専門外来を有する特定の医療機関に偏っている．なお精神科や神経内科を受診しても数ヶ月，ときに3年間も「うつ病」として漫然と治療されていたというケースが少なくなかった．

2）退職までの状況に関して

(1)療養のための有給休暇の利用

これについての有効回答は81あった．このうち民間会社に勤めていた47例については，利用の有無はほぼ半数ずつに分かれた．公務員の9例中，利用していたのは6例であった．

(2)解雇のプロセスの妥当性

発症に気付かれてから最終的に退職するまでに，配置異動や自宅でできる仕事の割り当てなどの配慮がなされたか否かを尋ねた．56の回答例のうち40例が，配慮が感じられたという意味で「概ね妥当」と回答していた．こうした結果からは，当事者が勤務していた民間会社には大企業が多いものと推測される．

3）生活の経済的基盤

ことに男性が40歳代，50歳代でこれらの疾患に罹患した場合，退職後に収入を失って経済的に困窮するのは必至である．これに対応する策としては，年金，生命保険などがある．

(1)障害年金の受給に関して

障害年金受給については，81回答のうち41例が受給ありと回答した．

(2)生命保険の高度障害認定に関して

生命保険においては，高度障害という概念がある．これに該当するのは，いわゆる寝たきりや植物状態あるいは絶対に回復が見込めない疾患に罹患している場合であり，死亡に準じて保険金が支払われる．ところが若年性認知症の場合，とくに

表3　若年性認知症患者の実態調査項目

- 受診・診断・告知
- 発病後の職場における処遇
- 経済的基盤
- 当事者・家族の要望

まだ身体的に健康である間は，認知機能障害が重篤であっても容易には高度障害と判定されないことが問題視されてきた．となると家族は保険金を得られないばかりか，掛け金を支払い続けなくてはならない．多くの場合，それが困難だから契約自体を解約せざるを得なくなる．

この高度障害の申請については24の回答があり，申請したのは12例であった．このうち3件で高度障害と認定されて支払いがなされていた．なされない9例では，その理由として「まだ身体機能が保たれていて障害は軽度」が多くあげられた．

なお筆者のこの1年以内の経験では，免責事項に該当するようなことがない限り，民間の生命保険であれば，ほぼ全例で高度障害と認められている．

4）聞き取り調査

介護上と療養生活の実態，および公的支援による処遇における課題を探るために筑波大学付属病院で予備調査を行なった．そこで得られた結果の中から，とくに大切と思われる家族からの要望を紹介する．

対象は，若年性認知症患者の家族21名（患者の基礎疾患はAD 10名，FTD 11名）である．なお当事者4名（男性2名，女性2名）にも回答してもらった．要望は以下のように要約される．

①応急対応をしてくれる専門施設
②若年性認知症者に対応できる通所施設
③本人の就労機会の拡大
④諸手続きの簡素化
⑤保険料等の優遇，免除措置の促進
⑥応需の経済支援
⑦見守りサポーターの充実
⑧家族に対するメンタル面のケア

以上の多くは，福祉・保健の問題である．しかし医療者も日常臨床において，こうした事柄へ配慮することは不可欠である．これまで以上に密な関連領域との連携が望まれる．

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Young-onset Dementia: An Unresolved Challenge

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Younger people with dementia present a unique challenge to modern Japanese society and those individuals who care for them. Although illnesses causing dementia occur much less commonly in younger than older people, it was estimated that there were about 30,000 affected younger people in 1995 in Japan. For younger people with dementia, effects on families, the presence of dependent young children, and the economic implications are particular challenges.

In this article, firstly, epidemiological findings regarding illnesses causing dementia in younger people were described. Secondly, the three major degenerative dementia forms that often develop in presenescence were reviewed.

Thirdly, the issue of service planning for such cases was discussed.

<Author's abstract>

<**Key words**: presenile dementia, epidemiology, Alzheimer, frontotemporal dementia, dementia with Lewy bodies>

The prevalence of illness causing presenile dementia: a four-center joint study in Japan

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Running title: The prevalence of illness causing presenile dementia: a four-center joint study in Japan

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Abstract

Aims: This study was designed to investigate the prevalence of illnesses causing presenile dementia using data from four memory clinics in Japan. **Methods:** A four-center joint study of presenile dementia patients whose age of onset was less than 65 years was performed. The presenile cases were retrospectively investigated using a series of demographic and clinical information. The diagnosis of dementia and that of subtypes had been made according to standard diagnostic criteria. **Results:** Among a total of 575 presenile cases, Alzheimer's disease (AD) was the most frequent (65%). Frontotemporal lobar degeneration (FTLD) was the second (13%), followed by vascular dementia (VaD; 5%), dementia with Lewy bodies (DLB)/ Parkinson disease with dementia (PDD; 4%). **Conclusions:** This large epidemiological study of presenile dementia shows the plurality of AD among the patients. The findings showed that FTLD and DLB/PDD were the second and third most common types of degenerative dementia in presenile dementia. The prevalence of FTLD was higher, while that of DLB/PDD was lower in the presenile cases in comparison with overall dementia cases. Contrary to some previous studies showing a high frequency of VaD, the proportion was relatively small in the

present study.

Introduction

In aging societies, individuals aged less than 65 years are expected to be actively involved in holding jobs, providing for families, and caring for children. Therefore, presenile dementia whose onset is less than 65 years creates a considerable psychological and economic burden on the patients and their families. Although this situation requires clinicians to have an understanding of presenile dementia [1], relatively little attention has so far been paid to it, in comparison to senile dementia.

A few studies address the incidence and prevalence of presenile dementia including early-onset Alzheimer's disease (AD) and other forms of dementia [2-6] (**Table 1**). However, the sample size of previous studies is relatively small; therefore, the prevalence of relatively rare causes of dementia such as dementia with Lewy bodies (DLB) and frontotemporal lobar degeneration (FTLD) remains unclear. To estimate the prevalence of common and rare illnesses causing presenile dementia, a four-center joint study was conducted in Japan using a larger number of samples in an attempt to gain sufficient accurate information.

It is unclear to what extent ethnicity is a variable in the prevalence of

these causative illnesses. The comparison of the APOE allele frequencies showed marked differences among the population of Western countries and Japan [7]. The pathoethiologic background of FTLD in Japan may be different from that in Western countries [8]. Such genetic and pathological differences may suggest a relationship between ethnicity and certain illnesses, but this issue has rarely been investigated. In this study an attempt was made to compare the results with previous data from Western countries.

Method

This retrospective study of patients with presenile dementia was performed using the data from clinical cases from four different outpatient memory clinics, including: The Department of Neuropsychiatry at Tsukuba U Hospital; the Department of Neuropsychiatry at Ehime U Hospital; the Department of Neurology at Fukuoka University Hospital; and the Department of Psychiatry at Musashi Hospital in the National Center of Neurology and Psychiatry. Each clinic specializes in the early diagnosis of dementia.

The subjects were diagnosed to have dementia at an age of less than 65 years between 2001 and 2007 at Tsukuba, 2000 and 2006 at Ehime, 2001 and

2006 at Fukuoka, and 1997 and 2001 at Musashi. A portion of the data from Ehime University Hospital has been reported elsewhere [9].

All the patients had been seen by experienced geriatric psychiatrists or behavioral neurologists. They underwent a series of physical and neurological examinations and were evaluated using a battery of neuropsychological tests. All of their caregivers were also interviewed. The age at onset was defined as the age when the earliest conclusive dementia symptoms was noticed by responsible caregivers.

All the patients underwent brain magnetic resonance imaging (MRI), except those with cardiac pacemakers who consequently underwent brain computed tomography (CT) instead. Almost all patients underwent SPECT except those who showed severe confusional state. The patients were also assessed using routine blood tests including vitamin B12, folic acid and thyroid function.

The diagnosis of dementia was made according to the Diagnostic and Statistical Manual of Mental Disorders, 4^{th} edition [10]. A diagnosis of probable AD was made according to the criteria of the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and

Related Disorders Association (NINCDS-ADRDA) [11], and vascular dementia (VaD) according to the criteria of the National Institute of Neurological Disorders and Stroke and the Association International pour la Recherché et l'Enseignement en Neurosciences (NINDS-AIREN) [12]. For the diagnoses of DLB, the consensus guidelines for the clinical diagnosis of DLB were employed [13]. According to the guidelines, patients who developed symptoms of Parkinsonism for 1 year or more prior to the onset of dementia were diagnosed as having 'Parkinson's disease with dementia (PDD)'. In the present study, the patients with PDD and DLB were included in the same category of PDD/DLB. FTLD was diagnosed according to the international consensus criteria [14]. Cases with dementia that did not meet any of above noted diagnostic criteria were classified into the category of "miscellaneous". A series of examinations were conducted after obtaining informed consent from the subjects and/or their caregivers. The ethical committee of each hospital approved this study.

Result

A total of 575 presenile patients, whose mean age at diagnosis was 58.3 ± 4.8 years were investigated. The age at onset of dementia for patients was

55.3 ± 4.8 years and the sex ratio was almost equal (M: F = 297:278).

Figure 1 shows the prevalence of illnesses causing presenile dementia for each participating hospital. AD was the most frequent cause of dementia (42-81%). FTLD was the second most common cause of dementia (10-23%) for three of the four hospitals, followed by VaD (4-10%), and DLB/PDD (1-3%). For one hospital, DLB/PDD was the second most common cause (14%), followed by FTLD (11%), DLB/PDD (3%) and others (3%). The prevalence of miscellaneous illnesses ranged from 3 to 26 %.

As shown in **Figure 2**, AD was the most frequent cause of dementia (65%) among the pooled subjects. FTLD was the second most common cause of dementia (13%), followed by VaD (5%) and DLB (4%). The category of "miscellaneous" included corticobasal degeneration (CBD), Creutzfeldt-Jakob disease (CJD), alcohol-related dementia, neurosyphilis, and so on. No difference was found in the sex ratio for these conditions, except for VaD patients (male dominance). The number of the patients increases with increasing age for each diagnostic category (**Table 2**).

Discussion

This retrospective study represents the largest epidemiological investigation of presenile dementia. Most of the previous epidemiological studies of presenile dementia were conducted at a single site; therefore, they had relatively small sample sizes [2-6] (**Table 1**). This four-center joint study is likely the largest survey of its kind. The clinic-based approach using consecutive clinical cases can diagnose rare diseases more accurately than pure cross-sectional or population-based studies. In addition, all diagnoses in this study were made according to the most recently established clinical diagnostic consensus criteria. Furthermore, almost all patients in this study underwent a series of extensive examinations including brain MRI and SPECT. Therefore, we believe the present study yields accurate and robust results.

In this study, the sex ratio is almost equal in three of the four dementing illnesses. The only exception is the male dominance for the patients with VaD (**Table 2**). It is well known that cerebrovascular disease shows male dominance, therefore, the male dominance of VaD appears to be reasonable. As expected, the number of patients increased with age, and most of the patients were diagnosed with dementia after age 45 for each category of dementia.

The prevalence of causative illnesses was different among the four

participating hospitals. A possible explanation for the inconsistency is a geographical bias. However, a more plausible explanation is the referral bias of the participating institutes. For example, patients with rare neurological diseases are expected to be referred to the department of neurology, whereas patients with FTLD characterized by behavioral and/or personality changes are likely to be referred to the department of psychiatry. Therefore, it may be assumed that a geographical and/or the referral bias might have affected the result of previous studies conducted at a single site. This explanation can also be applied to the differences between the current and previously reported data (**Table 1, Fig. 2**). Owing to the large sample gained from this four-center joint study, these biases may have been adjusted to some extent.

There are some noteworthy findings for each subtype of dementia in this study. The most frequent cause of dementia was AD. The plurality of AD has also been reported in previous reports from Western countries [2, 4-5], but the prevalence rate of the AD patients in the current study (65%) is higher in comparison to the results of the previous reports (34-53%) shown in **Table 1**.Several epidemiological studies from Western countries have reported that VaD was the first or second most common in presenile demented patients

(18-29%) [5-6]. On the contrary, the prevalence of VaD (5%) in the current study is lower than those of previous studies.

As described above, the participating sites of the present study are memory clinics. Although many stroke patients aged less than 65 years develop dementia, such patients are likely to be treated at institutions specializing in stroke, and not at memory clinics. Therefore, the difference in the specialty of the institutions conducting the study may account for the lower prevalence rate of VaD. Furthermore, VaD in Japan is characterized by high-frequencies of multiple lacunar type and Binswanger disease with a lower frequency of stroke episodes in these patients in comparison to VaD patients in Western countries [15]. These pathogenetic factors of VaD may also explain the lower prevalence of VaD, diagnosed according to NINDS-AIREN criteria [16]. Consequently, the lower prevalence of VaD may have contributed to the higher proportion of the AD in the current study.

In the current study, FTLD was the second most common degenerative dementia (13%). Many studies in Western countries have reported that FTLD is also second to AD among degenerative presenile dementia. The results of previous epidemiological studies from Western countries, shown in **Table 1**,

indicate that the average rate of FTLD was 12 % out of a total of 815 presenile cases [2-6]. Although familial cases comprise a certain portion of all FTLD patients in Western countries [17], the pathoethiologic background of FTLD of Japanese patients may be different from that of patients from Western countries [9]. In fact, almost all of the FTLD patients in the current study are sporadic cases. Nevertheless, the relatively high frequency of FTLD among presenile dementia is similar with that from Western countries. Although there is little epidemiologic data on DLB/PDD amongst clinical cases for presenile patients exclusively, exceptional studies from Western countries, as shown in **Table 1,** showed the average prevalence rate of DLB/PDD to be 4% [4-6]. Our prevalence rate of DLB/PDD (4%) therefore seems to be similar to that from Western countries.

We next examined the difference between the findings of the present study and data from previous research on both early- and late-onset dementia [18]. For the combined groups, it has been reported that more than 10% of all subjects were suffering from VaD [18]. The prevalence of VaD (5%) in our study is also lower than that of previous reports, probably because of the difference in the clinical situation where the study was conducted and the pathogenesis of

VaD. As for the prevalence of AD, it is reported that over 50% of all subjects with dementia show Alzheimer-type pathologic changes [18]. When considering the lower prevalence of VaD and consequent higher proportion of AD in our study, our value of 65% for AD among presenile dementia does not seem too different from that among overall dementia subjects. In comparison with the data for overall dementia showing a relatively lower rate of FTLD (5%) and a relatively higher rate of DLB/PDD (15%) [18], our results amongst presenile patients are characterized by a relatively higher prevalence of FTLD (13%) and a lower prevalence of DLB/PDD (4%).

We must refer to limitations of the present epidemiological study. First, it is not community-based but clinic-based, and therefore the results might not be representative. It is possible that more severe diseases are overrepresented, while milder dementias are underrepresented in a study based on memory clinics. Second, although all diagnoses of dementia causing illnesses in this study were made according to the established clinical diagnostic consensus criteria, the sensitivity and specificity of the criteria of DLB and FTLD have not fully been ascertained. For most cases, no autopsy was performed, so it was not possible to make the definite diagnoses. Third, there is a substantial difference in