responders, 122 final-nonresponders) except for 44 nursing home residents who were aged 65 years and older and who were registered in the LTCI system.

We compared the rate of LTCI use between the responders (i.e. quick-responders and delayed-responders) and final-nonresponders. We also compared the prevalence of dementia between LTCI users and non-users among the responders.

2.6. Statistical analysis

The criteria of MCI require the normative corrections for age, sex and years of education. For the normative data, we excluded the data from responders who did not complete the series of interviews and examinations of cognitive assessment, and from those who had a diagnosis of dementia, including the 44 nursing home residents. Consequently, we analyzed the data from 1,449 of 1,619 (89.5%) of quick-responders and 153 of 225 (68.0%) of delayed-responders. We calculated mean and SD for scores in each of the five cognitive domains after controlling for age, sex and years of education to classify MCI.

In epidemiological research, it is known that old-old subjects (those 75 or older) are the most difficult to recruit. Thus, age may be an important factor for estimating the cognitive states of non-responders. We determined the cognitive states for young-old (aged 65–74 years) and old-old (aged 75 years and older) groups separately.

We compared the prevalence of dementia and MCI between quick-responders and delayed-responders by using two cut-off values (1 SD and 1.5 SD). Comparison of the performance of the 5-Cog was also conducted.

We employed a t-test and chi-square test for continuous and categorical variables, respectively. A statistical significance level of 0.05 was used for all analyses. All analyses were performed using SPSS software version 15.0 (SPSS, Inc., Chicago, IL, US).

3. Results

3.1. The survey population

Of the 3,083 potential candidates, 132 were excluded (Fig. 1). Specifically, 87 had died and 45 had changed location before the initial examination. Additionally, 253 residents were uncontactable individuals. Thus, the remaining 2,698 residents were considered the candidates at the baseline. Of the 1,035 residents who refused to participate (non-responders), 225 became delayed-responders. Consequently, 1,888 (1,619 quick-responders, 225 delayed-responders, and 44 nursing home residents) (70.0%) of 2,698 baseline candidates were enrolled.

3.2. Demographics

Results of the baseline characteristics and clinical outcomes of quick-responders and delayed-responders along with the age and sex of nursing home residents are shown in Table 1. The results indicated that quick-responders were younger and more highly educated and showed better functioning than delayed-responders.

In addition, we also investigated age, sex and use of LTCI of final-nonresponders. These three variables were compared between final-responders (i.e. quick-responders and delayed-responders) and final-nonresponders. The final-nonresponders showed significantly higher rate in LTCI use, especially aged over 75 years (13.8% and 30.4%, respectively) ($p < 0.001$).

Table 1
Demographics and clinical data for the participants of the community-based survey

Characteristics	Participants total ($n = 1,888$) No. (%)	Quick-responders ($n = 1,619$) No. (%)	Delayed-responders ($n = 225$) No. (%)	Nursing home residents ($n = 44$) No. (%)	p value[b]
Age[a]	74.5 ± 6.6	74.1 ± 6.2	75.7 ± 7.5	84.0 ± 7.7	< 0.001***
Sex (% of women)	1137 (60.2)	962 (59.4)	147 (65.3)	28 (63.6)	0.090
Years of education[a]	9.8 ± 2.7	9.9 ± 2.7	9.0 ± 2.7	–	< 0.001***
GDS score[a]	3.0 ± 2.8	3.1 ± 2.8	2.4 ± 2.8	–	0.003**
N-ADL score[a]	48.7 ± 5.1	48.8 ± 5.0	47.9 ± 5.8	–	0.017*
BMI[a]	22.8 ± 3.3	22.8 ± 3.3	22.7 ± 3.3	–	0.657
Cerebral vascular disease	81 (4.5)	74 (4.6)	9 (4.0)	–	0.658
Hypertension	499 (27.5)	439 (27.1)	62 (27.6)	–	0.978
Diabetes mellitus	94 (5.2)	86 (5.3)	8 (3.6)	–	0.239
Smoking	630 (35.6)	563 (34.8)	67 (29.8)	–	0.979
Alcohol consumption	595 (33.6)	539 (33.3)	56 (24.9)	–	.247

GDS = Geriatric Depression Scale (higher score indicates more depressed state); N-ADL = N geriatric rating scale for activities of daily living (higher score indicates better function). *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

[a] Mean ± SD.

[b] Comparisons between quick-responders and delayed-responders.

Table 2
Comparison of the risk of dementia and mild cognitive impairment between quick-responders and delayed-responders

	Quick-responders ($n = 1619$)	Delayed-responders ($n = 225$)	Unadjusted models			Adjusted models		
	No. (%)	No. (%)	OR	95% CI	p value	OR	95% CI	p value
Dementia	60 (3.7)	19 (8.4)	2.40	1.40–4.10	0.001**	2.27	0.96–5.36	0.062
Age 65–74 years	13 (1.4)	2 (1.8)	1.31	0.29–5.90	0.723	1.72	0.23–13.12	0.599
Age 75 years or over	47 (6.8)	17 (14.7)	2.36	1.30–4.27	0.005**	2.42	0.92–6.39	0.075
MCI–1SD below	567 (38.9)	67 (47.2)	1.40	0.99–1.98	0.055	1.44	0.99–2.10	0.055
Age 65–74 years	301 (34.4)	37 (50.7)	1.96	1.21–3.17	0.006**	2.27	1.37–3.77	0.002**
Age 75 years or over	266 (45.7)	30 (43.5)	0.91	0.55–1.51	0.726	0.83	0.47–1.46	0.513
MCI–1.5SD below	276 (18.9)	28 (19.7)	1.05	0.68–1.62	0.822	1.19	0.75–1.87	0.458
Age 65–74 years	161 (18.4)	14 (19.2)	1.05	0.57–1.93	0.869	1.33	0.71–2.51	0.374
Age 75 years or over	115 (19.8)	14 (20.3)	1.03	0.56–1.92	0.917	0.97	0.50–1.88	0.924

For mild cognitive impairment (MCI) analyses, 1,457 quick-responders and 142 delayed-responders were included.
**$p < 0.01$.
Adjusted odds ratios (ORs) were calculated after controlling for age, sex, years of education, Geriatric Depression Scale (GDS) and Nishimura's Activities of Daily Living (ADL). CI = confidence interval, SD = standard deviation.

3.3. Dementia

As a result of the consensus diagnosis meeting, 60 quick-responders were identified as having dementia. We estimated the prevalence of dementia among quick-responders to be 3.7% (60/1,619). On the other hand, the second phase showed that 19 of the 225 subjects (8.4%) had dementia. Thus, the prevalence of dementia was significantly higher for delayed-responders than quick-responders ($p = 0.001$). In total, we estimated the overall prevalence of dementia in our community samples to be 6.5% ((60 + 19 + 44)/(1,619 + 225 + 44)), which is similar to the estimated dementia prevalence of 7.3% for the whole of Japan as of 2001 (Table 2).

3.4. Mild cognitive impairment

Among the samples with complete data for cognitive assessment, 1,457 quick-responders and 142 delayed-responders without loss of information on subjective memory complaint were included for this analysis. Using 1 SD and 1.5 SD cut-off values, 567 and 276 of 1,457 (38.9%, 18.9%) quick-responders and 67 and 28 of 142 delayed-responders (47.2%, 19.7%) were indicated to have some type of MCI, respectively. In order to examine the results more thoroughly, we used logistic regression analysis. As shown in Table 2, the rate of MCI (1 SD cut-off) was significantly higher for delayed-responders aged 74 or younger, even after controlling for age, sex, years of education, GDS score and ADL (adjusted odds ratio [OR] = 2.27, 95% confidence interval [CI]: 1.37–3.77, $p = 0.002$). The unadjusted OR for dementia was significantly higher in the old-old group; however, the significance disappeared after adjusting these variables.

3.5. Cognitive performance on five domains

We also compared cognitive function between quick-responders and delayed-responders after excluding individuals with dementia. The scores on memory function were significantly lower for delayed-responders than quick-responders, both in those aged 65–74 and over 75 years ($p < 0.001$ and $p = 0.039$, respectively).

Table 3
Distributions of dementia among the users of long-term care insurance

Long-term care insurance	Dementia No. (%)	Non-dementia No. (%)	p value
User	43 (30.5)	98 (69.5)	< 0.001
Non-user	36 (2.1)	1,667 (97.9)	

3.6. Long-Term Care Insurance

To provide further details on the non-responders, we also examined the data on LTCI. While 141 responders (131 of quick-responders and 10 of delayed-responders) proved to be the LTCI users, only 39 of these 141 provided complete data, which indicated that 102 of the 141 users were cognitively and/or physically so frail that they could not complete some of the examinations. We compared 141 LTCI users and 1,703 non-users among responders in terms of prevalence of dementia. The comparison revealed a significantly higher prevalence of dementia for the LTCI users (30.5%) than the non-users (2.1%, $p < 0.001$) (Table 3).

4. Discussion

Participation rate is one of the most important issues for an epidemiological study. We recruited 1,888 (1,619 quick-responders, 225 delayed-responders and 44 nursing home residents) of the 2,698 potential candidates. Participation rates of recent large studies, for example, the Amsterdam study of the Elderly[3] and the Canadian Study of Health and Aging[23] were 71.5% and 72.1%, respectively. Therefore, participation rate of our study (70.0%) appears to be acceptable.

We found that the prevalence of MCI (1 SD cut-off) was higher for delayed-responders aged 74 or younger. In contrast to previous studies,[3] the present study indicated that delayed-responders had a higher prevalence rate of dementia in the old-old group. The discordance is presumably attributable to methodological differences, namely recruitment of non-responders or assessment of cognitive functions. We, however, believe that non-responders in general are in lower cognitive states for the following reasons. First, the prevalence of LTCI use was significantly higher among final-nonresponders than the responders ($p < 0.001$). In addition, the LTCI data revealed that the prevalence of dementia was significantly increased in the LTCI users than the non-users among the responders (Table 3). These results suggest that the prevalence rate of dementia is higher in final-nonresponders.

It has been said that if a person is identified as having amnestic MCI, this subtype will have a high likelihood of developing Alzheimer's disease.[7] When compared with quick-responders in our study, delayed-responders had a 2.3-fold higher prevalence of MCI (OR = 2.27, 95% CI: 1.37–3.77) and significantly impaired memory function ($p < 0.001$). These results suggest that the delayed-responders have increased likelihood of MCI and developing dementia in later in life.

With regard to methodological issues, we used different settings of examining cognitive functions between quick-responders and delayed-responders. These differences might have affected the results. It has been said that face-to-face interaction is more effective than other methods in a health education area.[24] One of the reasons for the effectiveness of face-to-face interaction is that participants can receive timely feedback. Despite this advantage, delayed-responders exhibited significantly lower cognitive scores. Furthermore, we used only the data from 1,449 of 1,619 (89.5%) quick-responders and 153 of 225 (68.0%) delayed-responders for the normative data. However, the difference in the rate of use of data does not appear to have contributed to the poorer cognitive function observed among delayed-responders. The primary reason for the lower rate of delayed-responders (68.0%) was that many had such severe cognitive impairment that they could not complete the series of examinations. Thus, we may have overestimated cognitive functions of delayed-responders. Even with the possibility of overestimation, our results indicated lower cognitive function among delayed-responders.

The present study has some strength. While many of the previous similar studies[3,5] evaluated the cognitive function by using simple screening tests such as the Mini-Mental State Examination, we used an extensive cognitive test battery. Furthermore, we employed 1 and 1.5 SD cut-off using normative corrections for age, sex and years of education. These methods allowed us a more precise estimate of cognitive functions.

The present study also has limitations. One of the limitations is that the local welfare commissioners recommended individual residents for participation in the research, although the uncontactable individuals were excluded from the study. Excluding subjects and final-nonresponders may have produced distortions in the results. Nevertheless, we also confirmed the data regarding final-nonresponders including age, sex and LTCI use. Using the LTCI data made it possible to understand some basic characteristics of final-nonresponders. However, there is a possibility we may not be able to fully clarify the details of final-nonresponders. Second, we followed 8.3% (225/2,698) of delayed-responders. According to the previous research, approximately 6% to 14% non-responders were studied.[3,4,6] Moreover, Launer et al. attempted to collect 10% of all non-responders to clarify the characteristics and 8.5% of non-responders were studied.[3] In our study, 21.7% (225/1,035) of whole non-responders were followed. Thus, these delayed-responders could be compared with quick-responders. Third, we conducted a cross-sectional study. Further longitudinal study would be required to reveal a lifelong cognitive trajectory of non-responders.

In conclusion, we found that the prevalence of MCI was increased 2.3-fold in delayed-responders aged 74 or younger compared to the quick-responders. Our findings also suggest that non-responders are, in general, in lower cognitive states and have a higher prevalence of dementia. In order to develop services for persons with dementia, including early interventions, we must pay more attention to non-responders.

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妄想・異常行動

木之下 徹

Question & Answer

Q：BPSDに対する抗精神病薬を投薬する前に気をつけることは？

A：BPSDの医原性増悪や身体疾患の有無のチェック，あるいは体調，たとえば発熱，便秘，痛みなどの確認が必要である．そのほか対応のあり方でBPSDが生じていることもあり留意する．

Keyword：BPSD，医原性，心理社会的アプローチ，薬物療法

Case 1

BPSD(*J1*)に伏在するせん妄(*J2*)

患者：70歳代，男性．

脳血管障害＋アルツハイマー型認知症．認知機能障害は重篤であり簡単な応答のみ可能であった．家政婦との二人暮らし．数年前より易怒性を認め非定型抗精神病薬A薬を少量服用していた．ある日に起きあがれなく大声を発するとのことでA薬が1カ月間に9倍量処方された．しかし改善することなく，精神科に転科となり別の非定型抗精神病薬B薬が多量に追加処方された．介護者が不安になりさらに転科となり，元のA薬少量に減じられ，そのことでADLが改善し，大声を発することもなくなった．

このケースではBPSDに伏在するせん妄を，それとは気づかず抗精神病薬によって抑え込もうとしたことが，かえってADLを損ない精神症状を悪化させてしまう原因となった．われわれはこのような薬剤によるBPSDの増悪について留意しなければならなるい(*J3*)．

認知症の方の在宅療養のなかで，激しいBPSD(Behavioral and Psychological Symptoms of Dementia，認知症に伴う行動と心理の症状，*J1*)が出現することで，家族が苦しむことが多い．現在の日本において，BPSDが出現した際の受け皿となるべき社会資源が決定的に不足している．受療行動にも結び付き難く，本人を含む家族が社会から孤立しやすい．そういう状況の下では，BPSDを抑圧する対象としてみなしがちである．しかし

JIMノート

***J1*　BPSD**

認知症に伴う妄想，異常行動，幻覚，うつなどをBPSD(Behavioral and Psychological Symptoms of Dementia，認知症に伴う行動と心理の症状)という．これらを認知機能障害，すなわち中核症状と区別する態度形成は，認知症の臨床医療の最大の貢献であろう．

***J2*　せん妄**

しばしばBPSDに伏在するせん妄を見落としがちである．しかし多くのせん妄は別の原因があり，そのことでBPSDを一層増悪させる場合が多いことには留意する．

***J3*　BPSDの増悪要因**

BPSDの増悪要因として，身体疾患の伏在，BPSDあるいは身体疾患に対する薬剤，家族や介護者との関係性が挙げられる．それらを精査する以前に，その場のBPSDに対する安易な鎮静系薬剤の使用は避けるべきである．

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この視点は危険である．なぜ危険なのか，ということの理解はBPSD医療を行ううえで必須である．そしてこの視点の考察は非常に重要で，BPSDに対する処方内容のあり方そのものにも影響する．そのためまず本稿では，BPSDへの対応技術の前に，BPSDへの医療介入を行ううえでの視点について考察する．

妄想，異常行動への医療介入を行ううえでの視点

BPSDが出現すると，家族や介護スタッフなど，認知症高齢者を取り巻く周囲の人々はその対応が非常に困難になる．したがってBPSDは，関わる人々にとって好ましくない，抑圧すべき対象として認識されやすい．そのためBPSDへの医療介入を行う際には，BPSDという，普通ではない挙動を標的として，それをいかに抑えるかに視点が置かれがちである．しかしヒポクラテスの誓いにあるように，「医療は患者に害を及ぼしてはならない」としている．それにもかかわらず，BPSDへの医療介入を行う際にはBPSDを有する本人に対する救済というよりはむしろ，当人を取り巻く，当惑している周囲の人々に対する救済が行われがちである．実はその時，薬の過量投与や思わぬ副作用，身体疾患の見落としなどにより，BPSDが出現している当人に対して害を及ぼしがちである．

「医療並びに介護とは，その患者本人のためにある」というのは，まさに異論がないところであるが，BPSDを伴う認知症においてこれはしばしば崩れてしまう．ともすると身体拘束，化学拘束(薬物による拘束)を正当化してしまう事態になりかねない．困っていることを伝えている家族，介護者の救済のみ，という視点からの脱却を図り，当事者の視点で，そこから家族，介護者を含む全体的視点へのシフトが望まれる．

「目の前の認知症の本人は未来の私」という視点の導入

現在日本には認知症の方が約200万人おり，そう遠くない将来この数が倍になるだろうともいわれている．認知症の高齢者における有病率はきわめて高く(6～10%)，またBPSDの出現する可能性も高率である(8割～9割)[1]．すなわちBPSDを伴う認知症を抱えている人は，実は「明日の我が身」としても自然であろう．言い換えると，認知症を有する本人の視点とは，「目の前の認知症の人は未来の私」という視点である．

ここでもう少し具体的にこの視点を有するための方法論について，論じてみたい．仮に「今対面している認知症の方を自分だと思い，自分の欲目や周囲のしがらみを離れて，10秒間だけその人のことを考えてみる」ということを行うのである．まず「その方がもし自分だったら」という思いで，その方の置かれている状況を見てみる．そして再び本来の自分に戻り，その方が，他人の欲目，周囲のしがらみ，ご家族の希望などさまざまなものに囲まれていることに気づき，それらの周辺事情と，先ほど洞察した「認知症の本人の視点からの世界」をすり合わせる．そのすり合わせた結果をもって，次に行動計画を立てるのである．

「目の前の認知症の人は未来の私」のなかの「私」が満足しないようなケアや医療は，たとえそれがどんなに高尚で立派であっても，本人にとって何の意味もないものとなるだろう．言い換えると，本人の視点なき「質の高い医療」というのは，医療する側の都合で構成された「質の高い医療」であって，本人にとって必ずしも良い医療を保証するものではないのである．

Case 2

抑制系の薬が効く場合もあるが…

患者：80歳代，女性．

主訴：アルツハイマー型認知症による異常行動．

現病歴：暴言，暴力といったBPSDが激しく，老人ホームを8日で追い出された．そのため主治医はご自宅に訪問診療に出かけた．本人は食事を取ったことを忘れてすぐ要求する．その他興奮，妄想，徘徊，感情失禁，睡眠障害を認めた．「朝，おばあちゃんが迎えに来る」「家へ帰りますから，ここから帰してください」を繰り返し，出かける準備をして誰かを待っている仕草をしていた．夜間になると徘徊し，大声を出したり，4階の窓柵を越えようとするなどのBPSDの連続であった．高齢の夫は介護と睡眠不足に疲れ，遠方に住んでいる娘3人も交代で住み込み，目の離せない状態であった．そのためリスペリドン1 mg分2朝晩(液薬)で鎮静化を試みた．功を奏し，穏やかに暮らせるようになった．

このケースへの対応の問題点

介護者である夫自身が高齢で，いくら愛情があろうとも現実問題として支えきれない状態では，家庭崩壊そして心中や虐待の温床ともなり得る．地域においてこのようなケースにしばしば遭遇する．

果たして，この処方について問題はなかったか？ たまたまこのケースでは薬物療法が功を奏したわけであるが，必ずしもいつもそうとは限らない．その理由を以下に述べ，考えたい．

まず念頭に置くべきは，いま現れているBPSDが認知症そのものだけではなく，ほかの薬剤や身体疾患によるものによって増悪しているかもしれないという点である．ある報告[2]によると，BPSDの悪化要因には「薬剤によるものが37.7%」「身体合併症によるものが23.0%」「家族・介護環境によるものが10.7%」という結果が報告された．「薬剤によるもの」と「身体合併症によるもの」を合わせると，BPSDの悪化要因の6割になる．このことからもこのケースでは，薬物による鎮静化の前にまず全身状態の精査ならびに服薬しているすべての薬剤のチェックをすべきであった．このケースにおいては，もしかして発熱はなかったのか，便秘はどうであったのか，どこかに痛みはなかったのか，など身体の状況をあらかじめ最初につぶさに調べるべきであった．また同様に，ほかの薬剤についても，少なくても市販薬を含めて，服薬している薬をすべて調べ上げる必要があった．もしもBPSDが身体の状態や薬剤によって惹起されているものであれば，今回のような単なる薬剤による鎮静化ではかえってBPSDの悪化や身体症状の悪化に陥ることさえある．この際に，薬剤性，身体疾患に伴うせん妄との区別も重要となる．しかし現場ではこの区別は簡単ではない．対処のコツとしては常にせん妄を念頭に置きながら，これらの対応を行うことが推奨される．

また，BPSDが家族の対応に起因する場合もあるので注意が必要である．たとえば記憶障害を伴う人の場合，繰り返し介護者に同じことを質問するのだが，対応する側としてはあまりのしつこさに辟易し，つれない態度で対応してしまいがちである．その対応によって生じる対応関係の悪化が原因で暴言・暴力が出現する事例も枚挙にいとまがない．うまくその関係性が調整されれば薬剤による鎮静化などは不要となるであろう．

しかし，それでも，家族の悲痛な叫びに応じて，緊急回避的に薬剤を使用することがある．その際には上記のように身体疾患や薬剤性のせん妄が伏在している可能性があることを常に念頭に置きながら，とくにこれから行う薬剤療法におけるに副作用の出現に細心の注意を払うべきである．

妄想・異常行動に関する薬物療法

妄想・異常行動への投薬前の確認事項

妄想・異常行動に対する薬剤投薬は現在すべて保険診療において適応外である．したがってBPSDに対して薬剤を使用する際には，本人あるいは家族介護者に作用や有害事象のみならず，保険制度，負担金の問題，医療制度などについて詳しく説明し承諾を得る必要がある．

また，認知症を伴う虚弱な高齢者の場合，代謝回転が遅く，薬剤が身体に蓄積されやすい．さらに筋力低下により，足腰が弱っているなかで筋弛緩作用が出現することによって，転倒のリスクがきわめて高まる．したがって安易な睡眠薬や抗精神病薬などの投薬は慎むべきである．投薬する際には，各種トライアルによって得られた薬剤の作用時間を考慮し，体内に蓄積しないよう配慮すべきである．また仮に投薬するとしても，長期の漫然投薬は避けるべきである．当面不要と思われる薬剤は処方せず，BPSDの変化をある程度予見しながら，できるだけ少量かつ短期間で投薬を行うことを心がけるべきである．

随伴しがちな睡眠障害に対する薬物療法における一般的注意点

妄想・異常行動の背景に，しばしば睡眠障害が伴いやすい．しかし不眠といっても日中の覚醒レベルが低下していれば，当然夜眠れないことが容易に推論できる．また，覚醒リズムにおいて寝入りばなから体温が下がり，体温低下がその低下域の底から跳ね上がった段階で覚醒することが知られている．たとえば，電気毛布が高温のままでは入眠できないし，逆に体温が下がりすぎては覚醒してしまう．したがって生理的な覚醒リズムに影響を与える要因，たとえば，日中の覚醒レベル，体温，光刺激，ストレス，ほかの身体疾患などの見直しを含めた非薬物療法を第一に行うべきである．

自験例では，RBD(REM-Sleep Behavioral Disorders，レム睡眠時行動異常)がしばしば出現することで知られているレビー小体型認知症に対して，日中の覚醒レベルを上げるべくアリセプト®(適用外使用)を投薬することで，睡眠薬を使わずに良眠を得たケースもあった．夜間の不眠を解消するために日中のデイサービスを利用するなどの工夫によって，なるべく生理的な覚醒リズムを取るよう心がけたい．

以下，薬剤の認知症高齢者における一般的注意点について言及したい．

抗精神病薬に対する一般的注意点

抗精神病薬についての，非定形型と定形型との比較研究によれば，明らかに定形型のほうが非定形型よりも死亡リスクが高いことが示されている[3]．また，FDAによる認知症に対する抗精神病薬に関するWARNING PAPER[4]によると，非定形型抗精神病薬が約1.7倍だけ死亡のリスクを高めるとされている．この2つの報告を併せて考えれば，なるべく薬物療法は行わず非薬物療法を行うことが望ましい．しかしもし抗精神病薬を使う場合には，非定形型のほうがよいであろうということが示唆される．

抗精神病薬にしばしば認められる有害事象には，錐体外路症状(静座不能なアカシジア，異常な筋緊張が出現するジストニア，異常な不随意運動が出現するジスキネシアなど)，抗コリン作用(便秘，尿閉)，嚥下困難，薬剤の使い過ぎによる過鎮静，悪性症候群などがある．

抗パーキンソン薬に対する一般的注意点

この薬剤は，虚弱な認知症高齢者において，嚥下困難，意欲低下，食欲低下，錐体外路症状などに効果がある場合があり，しばしば使用される．しかしレビー小体型認知症や認知症を伴うパーキンソン病においては，抗パーキンソン薬でBPSD

を悪化させることも考慮する必要がある[5]．相対的に量が多すぎるとせん妄や精神症状が出現することもある．また，この薬剤の急激な中止は悪性症候群のリスクを高める．減量する場合には注意する必要がある．

抗てんかん薬に対する一般的注意点

脳血管障害ののちに処方されがちであるが，しばしば在宅療養では過量投薬となることもあり，日中から寝ているケースをよくみかける．急激な減量は痙攣を再燃するので慎重に調整すべきである．

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Long-Term Prognosis of Patients with Large Subcortical Infarctions

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Key Words
Prospective study · Ischemic stroke · Branch atheromatous disease

Abstract
Aim: We assessed the long-term prognosis of patients with large subcortical infarctions (LSCI). ***Methods:*** We defined LSCI as lesions ≥15 mm confined to deep penetrating arteries without a cardioembolic or atherothrombotic source. Patients with acute ischemic strokes were consecutively registered and followed for 751 ± 441 days. The clinical characteristics and long-term prognoses of patients with LSCI were compared to those of patients with lacunar (LACI), atherothrombotic (ATI) and cardioembolic infarctions (CEI). ***Results:*** At discharge from the hospital, the proportion of good outcomes (modified Rankin Scale ≤2) for patients with LSCI (52.1%) was similar to that for ATIs (47.2%), but worse than that for LACIs (73.2%). After a 3-year follow-up period, the mortality rates from LSCI, LACIs, ATIs and CEIs were 8.4, 8.2, 22.3 and 41.1%, respectively; the recurrence rates were 9.3, 14.1, 16.6 and 23.8%, respectively. ***Conclusions:*** The short-term prognosis of functional outcomes for LSCI was worse than that for LACIs, but similar to acute-phase ATI outcomes. The long-term prognosis after a LSCI is good, and recurrence tends to be lower than for LACIs.

Introduction

Infarctions with diameters ≥15 mm located in deep penetrating arteries are called giant lacunae or LSCI [1, 2]. In clinical practice, patients with LSCI who present with progressive stroke conditions (stroke-in-evolution) in the acute phase are encountered frequently. The presence of a LSCI is becoming increasingly important, despite the relatively small number of patients identified with the condition and the lack of clear clinical characteristics. A considerable number of LSCI show no apparent cardioembolic source or occlusion of major arteries. These types of LSCI are usually classified as giant lacunae, based on the criteria of the National Institute of Neurological Disorders and Stroke [3], or as 'strokes of undetermined etiology', based on the criteria of the Trial of Org 10172 in Acute Stroke Treatment [4]. The clinical characteristics of this condition, including the long-term prognosis, remain unclear. Therefore, understanding the pathobiology and etiology of LSCI may benefit patients who remain disabled as a result of these infarction events.

Two reports have described the long-term prognosis following LSCI [1, 5]. Donnan et al. [5] found that the rate of recurrent stroke or vascular death following a LSCI is approximately 2.7% per year during a mean follow-up

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period of 2.25 years. Halkes et al. [1] concluded that the rate of recurrence in patients with large subcortical infarcts (21%) does not differ from that in patients with cortical infarcts (22%) or small, deep infarcts (19%) after an average follow-up of 9.2 years in patients who had a transient or minor ischemic attack. No reports have described the long-term prognosis of LSCI compared with that of lacunar (LACI), atherothrombotic (ATI) or cardiogenic infarctions (CEI). Clarification of the long-term prognosis for patients with LSCI would be useful for prediction of death or recurrence of a cerebral infarction. Therefore, the purpose of this study was to determine the 3-year prognosis of patients with LSCI and compare outcomes for this type of stroke with those for other subtypes.

Subjects and Methods

Patients were registered in the Tottori University Lacunar Infarction Prognosis Study [6]. This study, started in 1999, was a collaborative effort with 3 central hospitals and 1 university hospital in the San-In district of western Japan. A total of 1,460 Japanese patients with acute ischemic strokes were consecutively registered over 3.5 years from December 1999 to May 2003. An acute ischemic stroke was defined as an infarction within 14 days of onset of symptoms. The mean period from stroke onset to admission was 1.5 days. Transient ischemic attacks were excluded from the registry. Registration data were gathered and statistically analyzed in the Department of Neurology at Tottori University.

Details gathered at registration included the following: gender; age; clinical conditions; brain imaging [head computed tomography (CT) and magnetic resonance imaging (MRI)]; intracranial vascular examinations [magnetic resonance angiography (MRA), 3-dimensional CT and angiography]; extracranial vascular examination (carotid ultrasonography); cardiac examinations [electrocardiography (ECG), transthoracic echocardiography and transesophageal echocardiography (TEE)]; determination of risk factors (hypertension, diabetes mellitus, dyslipidemia, smoking, heavy alcohol consumption and previous history of stroke); use of therapeutic medications (antiplatelet and anticoagulant therapy), and activities of daily living, assessed with the modified Rankin Scale (mRS) at hospitalization and discharge from the hospital.

Registration data were categorized according to specific criteria. Progression was defined as the presence of progressive clinical deficits or gradual deterioration after stroke onset. Progression was determined by neurologists at each facility. Risk factors have been described in detail previously [6]. Patients who were taking antiplatelet drugs or anticoagulants at the time of discharge from hospital were considered to be 'receiving treatment'. Antiplatelet drugs included aspirin, ticlopidine, cilostazol, dipyridamole, ibudilast, ifenprodil and nicergoline. At the time of this study, clopidogrel and dipyridamole had not been approved in Japan for treatment of ischemic stroke. Therapeutic drugs were administered at the discretion of the neurologist at each facility.

The specific examinations conducted were as follows: head CT, 1,460 cases (100%); MRI, 1,298 cases (88.9%); 3-dimensional CT, 22 cases (1.5%); angiography, 33 cases (2.3%); carotid ultrasonography, 1,181 cases (80.9%); ECG, 1,441 cases (98.7%); transthoracic ultrasonography, 1,103 cases (75.5%), and TEE, 101 cases (6.9%). Holter ECG monitoring was also performed in almost the same number of cases as TEE. Lesion size was investigated using diffusion-weighted imaging (DWI), T2-weighted imaging or fluid-attenuated inversion recovery (FLAIR) imaging (88.9%) or CT (11.1%). The mean duration from onset to imaging studies was less than 7 days.

Subtypes of ischemic stroke were classified according to the decision tree shown in figure 1 (modified from the National Institute of Neurological Disorders and Stroke Stroke Data Bank [3]). CEI was classified as an infarction with cardiogenic sources [4], based on the cardiac examinations. ATI was classified as an infarction lacking a cardioembolic source and with significant ($\geq$50%) stenosis or occlusion of the major arteries that supply the ischemic region, as observed via intra- or extracranial vascular examinations. LACI was classified as an infarction lacking a cardioembolic source and without significant ($\geq$50%) stenosis or occlusion of the major arteries that supply the ischemic region; these lesions were <15 mm in diameter in the subcortical or brainstem regions, as determined by imaging. LACI also included patients whose lesions were not revealed by imaging but who showed the classical lacunar syndrome as a clinical manifestation. Other brain infarctions of known etiology, consisting of infarctions caused by cerebral artery dissection or vascular inflammation, were excluded from the final analysis. Infarctions of uncertain cause (IUC) included those that could not be classified into one of the above categories. LSCI were defined as infarctions with a lesion $\geq$15 mm in diameter that was confined to one or a few penetrating branches in the subcortex or brainstem, without a cardioembolic source and without significant stenosis or occlusion of the major arteries that supply the ischemic region. The perfusion territories of the penetrating arteries were defined according to Tatu et al. [7, 8].

Follow-up continued until the patients dropped out of the study, died or could no longer be located. The mean duration of follow-up until death or dropout was 751 $\pm$ 441 days (median 1,095 days). Follow-up information was obtained from each participating research facility by a review of medical records, telephone surveys and mail-in surveys to the hospitals. Recurrence, subtype (if any) and cause of death (if any) were noted.

Statistical analyses were performed as follows. The χ^2 test was used to compare baseline characteristics, risk factors and therapeutic drug use. One-way analysis of variance was used to compare patient age and duration of hospitalization among the 4 stroke subtypes. Kaplan-Meier curves and log-rank tests were used to study mortality and recurrence rates among stroke subtypes. A Cox regression hazards model was used for stepwise multiple regression analysis. Values of $p < 0.05$ were considered to be statistically significant. All statistical analyses were performed using SPSS 15.0J software for Windows (SPSS Japan, Japan).

This study was conducted with the approval of Tottori University and the ethics committee at each participating institution.

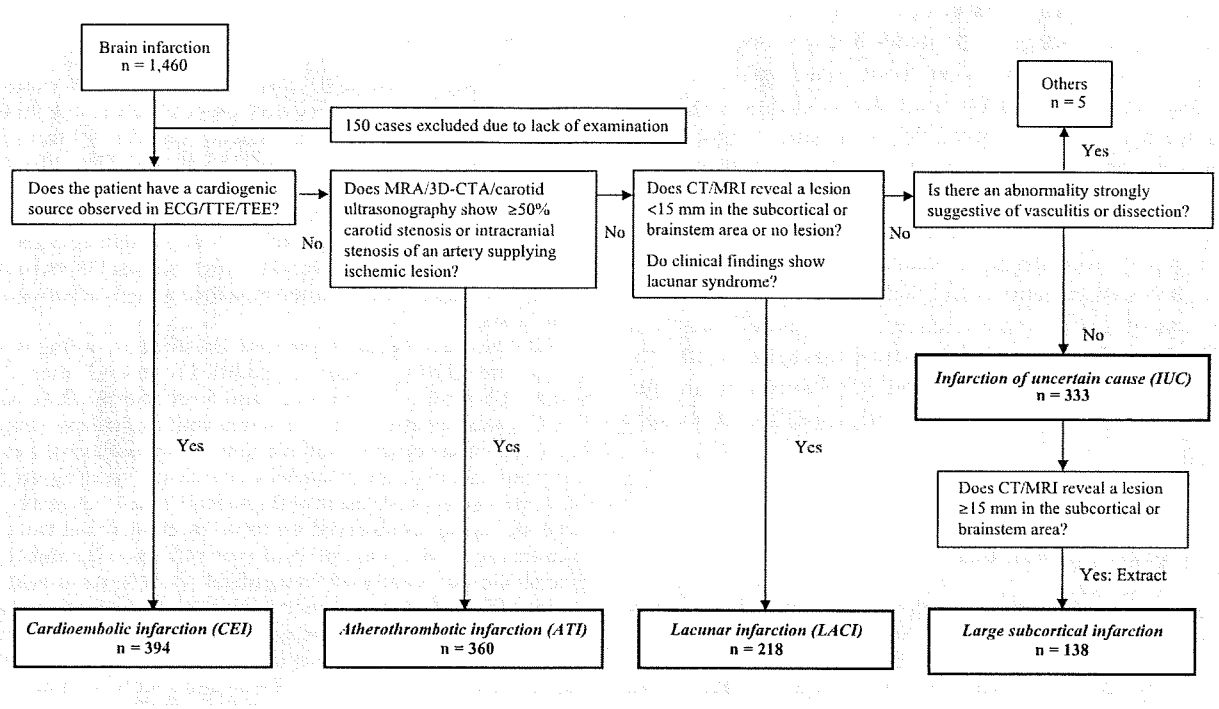

Fig. 1. Stroke classification (decision tree). TTE = Transthoracic echocardiography; 3D-CTA = 3-dimensional CT angiography.

Results

Among the 1,460 registered stroke cases, 150 cases could not be diagnosed due to insufficient data and were excluded. The remaining 1,310 cases were divided into 5 stroke subtypes (fig. 1). The frequencies of each subtype were as follows: CEI, 394 cases (27.0%); ATI, 360 cases (24.7%); LACI, 218 cases (14.9%); IUC, 333 cases (22.8%), and other brain infarctions of known etiology, 5 cases (0.3%). Careful analysis of the 333 IUC cases showed that 138 had LSCI (9.5%). These consisted of 109 infarcts located in the subcortex and 29 in the brainstem.

Baseline Characteristics of LSCI Compared to Other Subtypes

The baseline characteristics of the patients with LSCI are displayed in table 1. The majority of patients with LSCI were women. Compared to the other subtypes, the frequency of patients who had a history of stroke was lower, but the frequency with progressive temporal profiles at stroke onset was higher. Smoking was less frequent in patients with LSCI than in patients with ATIs or LACIs. Patients with LSCI showed a lower rate of disturbances in consciousness and cortical dysfunction compared with patients who had CEIs or ATIs. Regarding therapeutic drugs, 87.7% of patients with LSCI took antiplatelet drugs, similar to patients with ATIs or LACIs.

Short-Term Prognosis of LSCI

Short-term prognosis was assessed using the mRS at the time of hospitalization and discharge, taking into account the number of days spent in the hospital (table 1). Good outcomes (mRS ≤ 2) were seen for LACIs, LSCI, ATIs and CEIs, in descending order of frequency. Comparing the various subtypes by χ^2 tests, the proportion of good outcomes for LSCI (52.1%) was similar to that for ATIs (47.2%; $p = 0.67$), but was significantly worse than that for LACIs (73.2%; $p < 0.01$). In contrast, the proportion of deaths from LSCI (0.8%) was similar to that for LACIs (0%), but was better than that for ATIs (5.9%; $p < 0.01$). The duration of hospitalization for patients with LSCI was significantly lower than for ATIs and CEIs, but was significantly greater than for LACIs.

Table 1. Baseline characteristics of our patients

	CEI (n = 394)	ATI (n = 360)	LACI (n = 218)	LSCI (n = 138)	p value
Males	204 (51.8)	230 (63.9)	135 (61.9)	66 (47.8)	<0.01
Age, years (SD)	76.6 (10.3)*	71.2 (11.7)	70.9 (10.6)	71 (11.1)	<0.01[a]
Previous history of stroke	115 (29.7)	87 (24.4)	45 (20.6)	28 (20.4)	<0.05
Stroke in progress	86 (23.4)	131 (38.5)	64 (31.5)	67 (55.4)	<0.01
History of hypertension	255 (64.7)	251 (69.7)	152 (69.7)	102 (73.9)	0.18
History of diabetes mellitus	102 (26.1)	136 (37.8)	68 (31.5)	41 (29.7)	<0.01
History of dyslipidemia	119 (31.6)	149 (42.5)	98 (45.6)	60 (43.8)	<0.01
Smoking habit	67 (18.7)	118 (36.2)	74 (34.9)	26 (20.2)	<0.01
Heavy alcohol consumption	35 (9.5)	56 (17.0)	33 (15.6)	20 (15.4)	<0.05
Disturbance of consciousness	166 (42.1)	81 (22.5)	0	10 (7.2)	<0.01
Cortical dysfunction	167 (42.4)	115 (31.9)	0	6 (4.3)	<0.01
Cranial nerve finding	92 (23.4)	100 (27.8)	38 (17.4)	34 (24.6)	<0.05
Hemiparesis	298 (75.6)	268 (74.4)	184 (84.4)	124 (89.9)	<0.01
Ataxia	32 (8.1)	33 (9.2)	11 (5.0)	16 (11.6)	0.14
Sensory disturbance	50 (12.7)	66 (18.3)	64 (29.4)	27 (19.6)	<0.01
Antiplatelet drugs	138 (35.0)	291 (80.8)	190 (87.2)	121 (87.7)	<0.01
Anticoagulants	195 (49.5)	20 (5.6)	1 (0.5)	3 (2.2)	<0.01
mRS at hospitalization					<0.01
0–2	81 (21.7)	113 (33.1)	107 (54.0)	37 (31.4)	
3–5	292 (78.3)	228 (56.0)	91 (45.9)	81 (68.6)	
3	19 (5.1)	26 (7.6)	22 (11.1)	23 (19.6)	
4	20 (5.4)	41 (12.0)	42 (21.2)	22 (18.7)	
5	253 (67.8)	161 (47.2)	27 (13.6)	36 (30.6)	
mRS at discharge					<0.01
0–2 (good outcome)	138 (36.6)	160 (47.2)	142 (73.2)	62 (52.1)	
3–5 (poor outcome)	183 (48.6)	159 (46.9)	52 (26.8)	56 (47.1)	
3	48 (12.7)	58 (17.1)	33 (17.0)	35 (29.5)	
4	56 (14.9)	53 (15.6)	14 (7.2)	12 (10.2)	
5	79 (21.0)	48 (14.2)	5 (2.6)	9 (7.7)	
6 (death)	56 (14.9)	20 (5.9)	0	1 (0.8)	
Hospital stay, days (SD)	50.7 (50.0)*	51.8 (54.9)*	25.7 (28.1)*	40.1 (31.7)	<0.01[a]

Values represent numbers of patients with percentages in parentheses, except where indicated otherwise. p values were determined by χ^2 test, except where indicated otherwise. * $p < 0.05$ versus LSCI (Dunnett's post hoc test).

[a] Determined by analysis of variance.

Long-Term Prognosis of Patients with LSCI

Long-term prognosis was assessed by stroke recurrence and death. Over a 3-year period, 248 deaths were recorded. The survival curve is shown in figure 2. The mortality for each subtype was as follows: LSCI, 10 cases (8.4%); LACI, 16 cases (8.2%); ATI, 71 cases (22.3%), and CEI, 151 cases (41.1%). Hazard ratios (HRs) are shown in table 2. Stepwise multiple regression analysis identified age, gender and diabetes mellitus as independently associated with mortality. After adjusting for these factors, mortality over 3 years for LSCI was lower than that for CEIs [HR 4.26, 95% confidence interval (CI) 2.23–8.14; $p < 0.01$] or ATIs (HR 2.07, 95% CI 1.05–4.07; $p < 0.05$) and similar to that for LACIs (HR 0.72, 95% CI 0.32–1.62; $p = 0.42$). Causes of death in patients with LSCI included infection in 5 cases (pneumonia in 4, sepsis in 1), malignancy in 2 cases, renal failure in 1 case, acute posttraumatic subdural hematoma in 1 case and an unknown cause in 1 case.

Over the 3-year period, 155 stroke recurrences were observed. Recurrence-free survival is shown in figure 2. The number of recurrences for each subtype was as follows: LSCI, 11 cases (9.3%); LACI, 28 cases (14.1%); ATI, 48 cases (16.6%), and CEI, 68 cases (23.8%). Stepwise multiple regression analysis showed that age and previous history of stroke were independently associated with re-

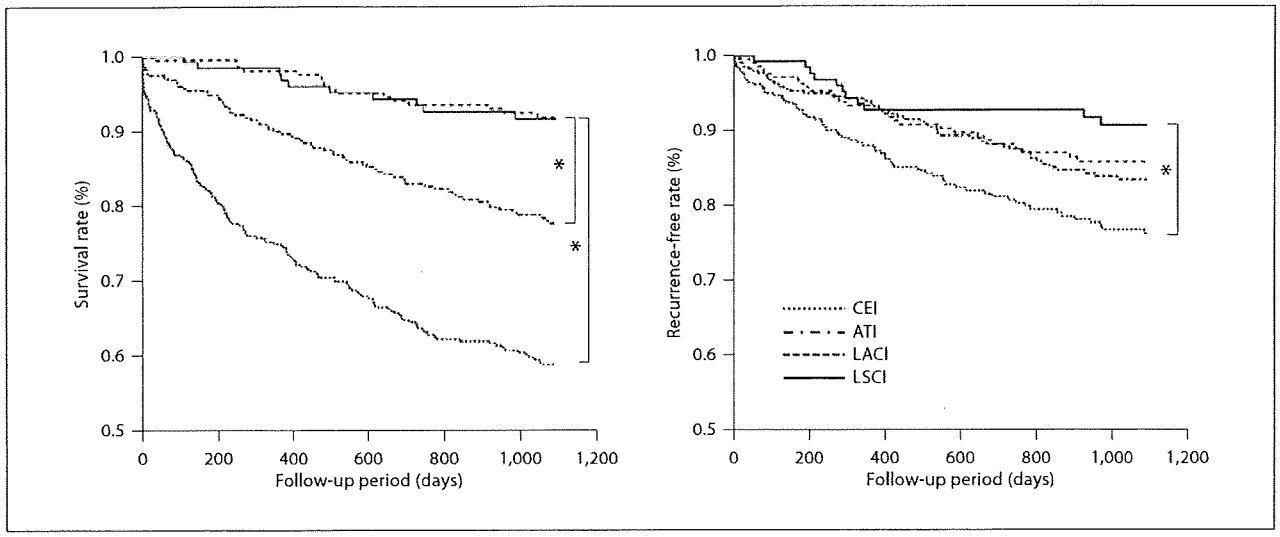

Fig. 2. Kaplan-Meier estimates of survival rates and recurrence-free rates for the 4 stroke subtypes. The survival rate of patients with LSCI showed no significant difference compared with LACIs ($p = 0.93$), but was higher than that for patients with ATIs ($p < 0.01$) and CEIs ($p < 0.01$). The survival rate for LACIs was also higher than that for ATIs ($p < 0.01$) and CEIs ($p < 0.01$). The recurrence-free rate of LSCI did not differ significantly compared to that of LACIs ($p = 0.31$) and ATIs ($p = 0.22$), but was higher than that of CEIs ($p < 0.01$). * $p < 0.01$.

Table 2. HRs and 95% CIs for death and recurrence of stroke over a 3-year follow-up period comparing LSCI with other subtypes

	CEI	ATI	LACI	LSCI
Death				
Number of patients (events)	394 (151)	360 (71)	218 (16)	138 (10)
Crude HR (95% CI)	6.15 (2.86–13.20)	2.46 (1.11–5.43)	1.05 (0.42–2.63)	1.00
p value	<0.01	<0.01	0.94	
Adjusted HR[1] (95% CI)	4.26 (2.23–8.14)	2.07 (1.05–4.07)	0.72 (0.32–1.62)	1.00
p value	<0.01	0.04	0.42	
Recurrence				
Number of patients (events)	394 (68)	360 (48)	218 (28)	138 (11)
Crude HR (95% CI)	2.80 (1.33–5.88)	1.53 (0.71–3.30)	1.51 (0.67–3.40)	1.00
p value	<0.01	0.08	0.21	
Adjusted HR[2] (95% CI)	2.59 (1.32–5.07)	1.54 (0.77–3.10)	1.48 (0.71–3.06)	1.00
p value	<0.01	0.23	0.30	

[1] Adjusted for age, gender and diabetes mellitus. [2] Adjusted for age and previous history of stroke.

currence. After adjusting for age and previous history of stroke, the recurrence rate of LSCI was lower than that of CEIs (HR 2.59, 95% CI 1.32–5.07; $p < 0.01$), but was not significantly different from that of ATIs (HR 1.54, 95% CI 0.77–3.10; $p = 0.23$) or LACIs (HR 1.48, 95% CI 0.71–3.06; $p = 0.30$). The recurrence rate of LSCI was the lowest among the 4 categories, and a significant difference was found when compared to that of CEIs (table 2). Clinical subtypes that were associated with the recurrence of LSCI included LACIs (5 cases) and IUCs (2 cases). In 4 cases, insufficient data were available for determination.

Discussion

In this study, we analyzed the long-term prognosis of patients with LSCI. We determined that the clinical characteristics of LSCI result in poor functional outcomes, similar to acute-phase ATI, and a good prognosis, similar to chronic-phase LACI. Patients suffering from LSCI display this biphasic clinical course, which is seen in 10% of all patients with ischemic stroke. Thus, LSCI may be considered to be a distinct stroke subtype.

Patients with large subcortical infarcts reportedly show cardiogenic sources in 9–52% of cases [5, 9–14] and stenosis of major arteries in 27–89.5% of cases [2, 5, 9–16]. We stress that a cardiac source or stenosis of major arteries can cause a LSCI. Therefore, a LSCI with a cardiogenic source should be classified as a CEI, and a LSCI with significant (≥50%) stenosis or occlusion of the major arteries that supply the ischemic region should be categorized as an ATI.

Our results indicate that patients with LSCI do not usually experience recurrent episodes over the long term. LSCI may be caused by atheromatous disease in the penetrating branch arteries [17]. Branch atheromatous disease completely occludes the penetrating arteries; therefore, recurrence in these arteries is not common. This mechanism may be responsible for the low recurrence rate associated with LSCI.

Our results indicate that patients with LSCI experience a severe initial attack. LSCI often involve the striatocapsular region and pyramidal tract. The clinical data revealed that approximately half of the patients showed a progressive pattern at onset (55.4%), and some of them displayed disturbances in consciousness (7.2%) or cortical dysfunction (4.3%). LSCI were associated with worse mRS than LACIs. Such a progressive pattern may be related to stroke severity.

We acknowledge that this study has several limitations. Firstly, the accuracy of subtype classification is limited. In our study, the implementation rate of TEE was low, because we performed TEE after assessing the potential risks and benefits to patients and the condition of patients in acute care hospitals. In 40–60% of cases in which TEE is performed, a cardiac source of embolism is identified [18–20]. The possibility that other stroke subtypes (ATI, LACI or IUC) were categorized as CEI in the assessment cannot be ruled out. In addition, the rate of Holter monitoring was almost as low as the rate of TEE. The Holter ECG offers a low detection rate of 2–3% for new-onset atrial fibrillation in acute stroke [21]. Therefore, the Holter monitoring rate had an insignificant effect on the diagnosis of CEI. However, despite this limitation, we were able to identify differences between the long-term prognosis for LSCI and that for CEI or ATI. In our opinion, applying our examination system in routine clinical practice could clarify the clinical characteristics of LSCI. We also evaluated lesion size using DWI or FLAIR in 88.9% of cases and CT in the remaining cases during the early stage after onset. A lesion ≥15 mm in diameter on DWI could actually be <15 mm in diameter, as the apparent size of a lesion in acute ischemic infarction appears larger on DWI due to edema. Lee et al. [22] reported that the use of DWI/MRA within 24 h of hospitalization substantially improves the accuracy of diagnosis of the early ischemic stroke subtype, and that diagnosis by DWI/MRA within 24 h is the same as the final diagnosis in 94% of cases. Our diagnosis of the stroke subtype using DWI or FLAIR was thus fairly accurate; however, a few cases of LACI may have been classified as the LSCI subtype. Secondly, patients at each facility were managed using nonstandardized treatment protocols, and their effects on survival and recurrence remain unknown. Thirdly, our investigation was limited to the assessment of survival and recurrence, and we did not assess activities of daily living during the 3-year period. Thus, future studies should also include assessment of activities of daily living.

Summary

The short-term prognosis of functional outcomes of LSCI is poor, similar to that of ATIs in the acute phase. However, mortality and recurrence rates for LSCI are low, resembling those for LACIs. This information on the prognoses of patients with LSCI should prove helpful to medical staff and patients who remain disabled due to this condition.

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