and non-converters, AD converters demonstrated more enhanced hypoperfusion bilaterally in the temporo-parietal area, medial temporal area, and posterior cingulate and precuneus. These data parallel and strengthen results of previous studies [9–20].

The present study had some limitations. First, the neuropsychological test batteries were limited and did not include tests specifically designed to assess cognitive functions for early diagnosis of AD. However, MMSE and WMS-R-LM were more practical as a routine clinical scenario. Second, the primary outcome (conversion to AD) contained some degree of error because some patients classified as non-converters may have converted to AD with a longer follow-up.

Conclusions

^{123}I-IMP-CBF SPECT with both automated ROI analysis and central image interpretation was sensitive but relatively nonspecific for prediction of clinical outcome during the 3-year follow-up in individual amnestic MCI patients. A combination of statistically significant predictors, both SPECT with automated ROI analysis and neuropsychological evaluation such as MMSE and WMS-R-LM, may increase predictive utility.

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Respiratory dysrhythmia in dementia with Lewy bodies: a cross-sectional study

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ABSTRACT

Objectives: Dementia with Lewy bodies (DLB) is the second most common form of neurodegenerative dementia after Alzheimer's disease (AD). DLB is characterised by intracytoplasmic inclusions called Lewy bodies that are often seen in the brainstem. Because modulation of the respiratory rhythm is one of the most important functions of the brainstem, patients with DLB may exhibit dysrhythmic breathing. This hypothesis has not yet been systematically studied. Therefore, we evaluated the association between DLB and dysrhythmic breathing.

Design: In this cross-sectional study consecutive inpatients who were admitted for the evaluation of progressive cognitive impairment were enrolled. We assessed breathing irregularity using polysomnographic recordings on bed rest with closed eyes, without reference to the clinical differentiation among DLB, AD and having no dementia.

Setting: Single centre in Japan.

Participants: 14 patients with DLB , 21 with AD and 12 without dementia were enrolled in this study.

Primary outcome measures: The coefficient of variation (CV) of the breath-to-breath time was calculated. We also examined the amplitude spectrum A (f) obtained using the fast Fourier transform and Shannon entropy S of A(f) in patients with DLB compared with patients with AD and patients without dementia.

Results: The values of CV and entropy S were significantly higher in patients with DLB than in patients with AD and patients without dementia. No significant differences were observed between patients with AD and patients without dementia.

Conclusions: Patients with DLB exhibit dysrhythmic breathing compared with patients with AD and patients without dementia. Dysrhythmic breathing is a new clinical feature of DLB and the spectral analysis of breathing patterns can be clinically useful for the diagnostic differentiation of DLB from AD.

ARTICLE SUMMARY

Strengths and limitations of this study

- Dysrhythmic breathing is a completely novel topic in DLB.
- This study is a cross-sectional, small-sized pilot study.
- The patholocgical diagnosis of DLB could not be obtained.

INTRODUCTION

Dementia with Lewy bodies (DLB) is a neurodegenerative disease characterised by parkinsonism, visual hallucinations and cognitive fluctuations. DLB is now thought to be the second most common form of dementia after Alzheimer's disease (AD), affecting 15–25% of elderly demented patients.[1] The clinical diagnostic criteria for DLB were first published in 1996 and modified in 2005.[1 2] The central feature of DLB is progressive cognitive decline. The core features include recurrent visual hallucinations, spontaneous features of parkinsonism and fluctuating cognition with pronounced variations in attention and alertness. These diagnostic criteria require clinical evaluation by a trained neurologist and include few objective markers. Although Single Photon Emission CT (SPECT) and ^{123}I-metaiodobenzylguanidine (MIBG) myocardial scintigraphy are useful for making the differential diagnosis of DLB,[3–5] these examinations are too expensive to be generally utilised. DLB is characterised by intracytoplasmic inclusions called Lewy bodies that consist of filamentous protein granules composed of α-synuclein and ubiquitin. Lewy bodies are often seen in the brainstem and in limbic and cortical neurons.[2] However, the brainstem serves as the connection among the cerebral hemispheres and the cerebellum, and is responsible for basic vital functions. Modulation of the respiratory rhythm is one of the most important functions of the brainstem. In cases of brain disorders, such as Wallenberg syndrome and brain tumours, it is known that respiratory patterns sometimes become ataxic. Because brainstem neurodegeneration is often

seen in patients with DLB, the respiratory patterns of patients with DLB might be dysrhythmic. However, this hypothesis has not yet been systematically studied and no controlled data have been published to date. The current investigation was performed in patients with DLB, AD and patients without dementia to assess and compare breathing patterns. In addition, we evaluated the usefulness of the measurement of breathing patterns as a novel tool to aid the differential diagnosis of dementia.

METHODS

Subjects

The study population comprised consecutive inpatients of the Department of Geriatric Medicine at the University of Tokyo Hospital, who were admitted for evaluation of progressive cognitive impairment. The patients underwent neuropsychological assessments, including the Mini-Mental State Examination (MMSE), blood tests and neuroimaging tests (MRI and SPECT). The diagnosis was performed at a consensus conference of physicians and neurologists. The diagnosis of DLB was based on the clinical diagnostic criteria proposed by McKeith *et al*.[2] And AD was diagnosed in accordance with the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's disease and Related Disorders Association.[6] The group without dementia comprised patients who did not fit the criteria for dementia in the medical and neurological examinations. Between November 2010 and June 2012, 70 patients were enrolled in this study.

Exclusion criteria

We evaluated the breathing patterns of patients with DLB, with AD and patients without dementia. Patients with cognitive impairments other than AD or DLB (eg, normal pressure hydrocephalus and vascular dementia) were excluded.

Breathing irregularities are associated with certain environments such as high altitudes, medical conditions, such as heart failure and chronic obstructive pulmonary disease, and the usage of opioids or levodopa.[7 8] We excluded one patient who reported breathing problems, including dyspnoea. We also excluded four patients who were taking levodopa and dopamine agonists. No patients were using opioids. We excluded three patients whose recorded respiratory signal data were insufficient due to noise.

Recordings of respiration

The patients underwent 30 min or more of recordings of respiration on bed rest with closed eyes in the inpatient ward by using the device for polysomnography (Somnotrac Pro, CareFusion, San Diego, California, USA). The recordings included two EEG leads (C3-A2 and O2-A1), electro-oculogram and submental electromyogram (EMG). Oronasal thermistor channel and arterial oxygen saturation (finger oximetry) were also monitored. All recordings were scored visually by an experienced rater according to the standard criteria.[9]

Five consecutive minutes of stable respiratory signals measured while the patients were awake were extracted from the recordings. Stable respiratory signals during wakefulness were identified using the respiratory signals themselves, arterial oxygen saturation, EMG and EEG. Wakefulness was confirmed using EEG. When the amplitude of the EMG signal that detected any body movements was high, that part of the signal was considered to have occurred during movement and was determined to be inappropriate for analysis. Epochs including apnoeas and hypopneas were also excluded.

Analysis of respiratory signals

Five minutes of stable respiratory signals were analysed. The breath-to-breath time was calculated for each respiration. To assess breathing irregularities, the coefficient of variation, CV ((SD/mean)×100) for the breath-to-breath time was calculated. The respiratory rate was also calculated.

In addition, we examined the amplitude spectrum A(f) obtained using fast Fourier transform (FFT) for analysing oscillation patterns in the respiratory signals. A(f) represents the amplitude distribution as a function of frequency. To avoid the possibility of spectral leakage, the signals were windowed by multiplying them by a Hamming window (w(n)):

$$w[n] = 0.54 - 0.46\cos(2\pi n/N) \text{ for } n = 0, 1, 2, \ldots, (N-1)$$

Then, the amplitude spectrum of the respiratory signals was analysed using the FFT of the Hamming-windowed signal.[10] Furthermore, according to Shannon entropy, we determined the spectral entropy S based on normalised A (f) to assess breathing irregularities:

$$\text{Entropy } S = -\sum A(f) \times \log_2(A(f))$$

To reduce the influence of artifact in the respiratory signals and FFT, we restricted the frequency of analysing Shannon entropy. Based on the results of the breath-to-breath time analysis (1.7–7.6 s, namely 0.13–0.59 Hz), we determined the validated frequency of 0.1–0.6 Hz.

Statistical analysis

The distribution of data was examined using the Shapiro-Wilk test. If data were normally distributed, one-way analysis of variance with Games-Howell post hoc tests was applied for group comparisons. If the data deviated significantly from normality, the Kruskal-Wallis test was used, followed by evaluation with the Mann-Whitney U test for multiple comparisons, with the p values being corrected according to the Bonferroni method. In correlation analysis, the Spearman rank

correlation coefficient was used. The χ^2 test was used to compare categorical variables, such as gender.

The diagnostic cut-off points for the CV value and Shannon entropy S to discriminate between DLB and AD were estimated for each outcome by maximising the Youden index. The discrimination ability was assessed by the area under the curve (AUC). Using this threshold, the sensitivity and specificity were calculated.

All of the statistical analyses were performed using the SPSS software program (V.19.0, SPSS inc, Chicago, Illinois, USA). Statistical significance was defined as p values <0.05.

RESULTS

Patient characteristics

Fourteen patients with DLB, 21 with AD and 12 without dementia were enrolled in this study. Among the 14 patients in the DLB group, 9 patients had probable DLB and 5 patients had possible DLB. The diagnoses in the five possible DLB patients were all supported by the typical findings in SPECT: generalised low uptake, reduced occipital activity and relatively preserved hippocampal blood flow. Table 1 shows the characteristics of the patients. The age and sex distributions were not significantly different among the three groups. No significant difference was found between the DLB group and the AD group in the MMSE. The use of medications for hypertension, hyperlipidaemia and diabetes mellitus were similar between the groups. Four patients in the DLB group, five patients in the AD group and no patients in the group without dementia had taken donepezil.

Breathing patterns

Figure 1 shows examples of flow signals during wakefulness for a patient with DLB, with AD and without dementia. Figure 2 shows examples of the characteristic patterns of the amplitude spectrum A(f). The patient with AD and without dementia exhibited a sharp peak in the spectrum. However, the amplitude spectrum of the patient with DLB was distributed over the whole displayed frequency area. These tracings indicate the occurrence of more irregular breathing patterns in the patient with DLB compared with that observed in the patient with AD and the patient without dementia.

The respiratory rates calculated from the average breath-to-breath time in patients with DLB, with AD and patients without dementia were 16.2 (3.2), 17.7 (2.7) and 18 (2.3)/min, respectively (mean (SD)). These differences were not statistically significant. However, the CV value for the breath-to-breath time in patients with DLB was significantly higher than in either the patients with AD or the patients without dementia (13.5 (2.6), 10 (3) and 9.9 (2.8), respectively; figure 3A). To discriminate the patients with DLB from those with AD using the CV value, the most favourable diagnostic threshold was found to be 10.2 (AUC=0.79). This threshold had a sensitivity of 92.9% and a specificity of 61.9%.

The results of the comparison of Shannon entropy S are summarised in figure 3B. The values of Shannon entropy S were significantly higher in patients with DLB than in patients with AD and patients without dementia (6.35 (0.11), 6.11 (0.29) and 6.16 (0.19), respectively). To discriminate patients with DLB from those with AD using the Shannon entropy S value, the most favourable diagnostic threshold was found to be 6.18 (AUC=0.77). This threshold had a sensitivity of 100% and a specificity of 57.1%.

These findings indicate the diversity of breathing frequencies, that is, respiratory dysrhythmia, in patients with DLB.

Comparison of CV and Shannon entropy S

To assess breathing irregularities, we used two different methods, namely, we compare CV and Shannon entropy S. These two methods are independent approaches to the assessment of breathing patterns; however, a significant correlation (Spearman r=0.78, p<0.001) was observed between these two values (figure 4).

DISCUSSION

In this study, we observed that patients with DLB exhibit dysrhythmic breathing compared to patients with AD and patients without dementia.

Table 1 Characteristics of patients with DLB, with AD and without dementia

Characteristics Number of patients	Patients with DLB n=14	Patients with AD n=21	Patients without dementia n=12	p Value
Age (years)	81.5 (5.6)	79.6 (7.8)	78.5 (4.3)	n.s.
Sex (men/women)	6/8	7/14	4/8	n.s.
MMSE	21.0 (3.8)	21.2 (3.4)	27.8 (2.1)	<0.001*
Hypertension	4	9	3	n.s.
Hyperlipidaemia	2	1	0	n.s.
Diabetes mellitus	1	1	1	n.s.

Values expressed as mean (SD) or number.
*One-way analysis of variance with Games-Howell post hoc tests (DLB vs AD: n.s., DLB vs without dementia: p<0.001, AD vs without dementia: p<0.001)
AD, Alzheimer's disease; DLB, dementia with Lewy bodies; MMSE, Mini-Mental State Examination; n.s., not significant.

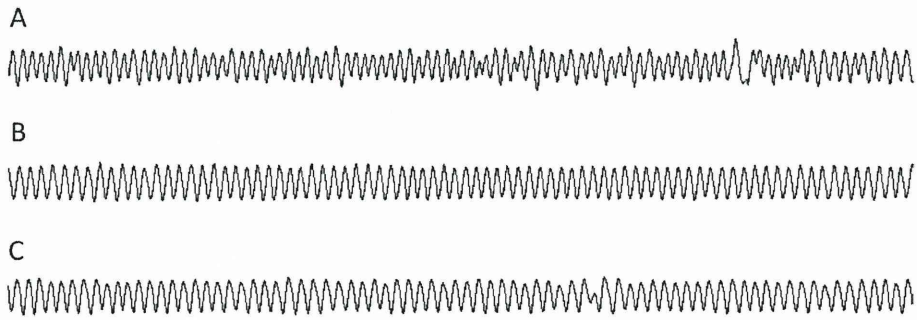

Figure 1 Typical flow patterns of a patient with DLB (A), a patient with AD (B) and a patient without dementia (C) observed in epochs of 5 min. Respiratory pattern is more irregular in the patient with DLB as compared with the patient with AD and the patient without dementia. AD, Alzheimer's disease; DLB, dementia with Lewy bodies.

The modulation of the respiratory rhythm is closely associated with the brainstem.[11] In particular, the pre-Bötzinger complex (pre-BötC) and the retrotrapezoid nucleus/parafacial respiratory group (RTN/pFRG) are thought to be very important for respiratory rhythm regulation.[12–14] For this reason, respiratory dysrhythmia may occur in cases of brainstem disorders, such as Wallenberg syndrome and brain tumours. In patients with DLB, Lewy bodies are often seen in the brainstem; however, it remains unknown whether the localisation and density of Lewy bodies are strongly associated with the symptoms of DLB. It is possible, considering the neurodegenerative aspects of DLB, that localisation of Lewy bodies in the brainstem causes respiratory dysrhythmia. One report has indicated that visual hallucinations are associated with increased numbers of Lewy bodies in the temporal lobe and amygdala, each of these areas being implicated in the generation of complex visual images.[15] In addition, concerning the association between respiration and DLB, Mizukami *et al*[16] reported the occurrence of decreased ventilatory responses to hypercapnia in patients with DLB. Furthermore, respiratory insufficiency, sleep-disordered breathing and central respiratory failure are known to occur in patients with multiple system atrophy,[17 18] which is an α-synucleinopathies, similar to DLB.

In this study, we also analysed the breathing patterns of patients without dementia. The CV for

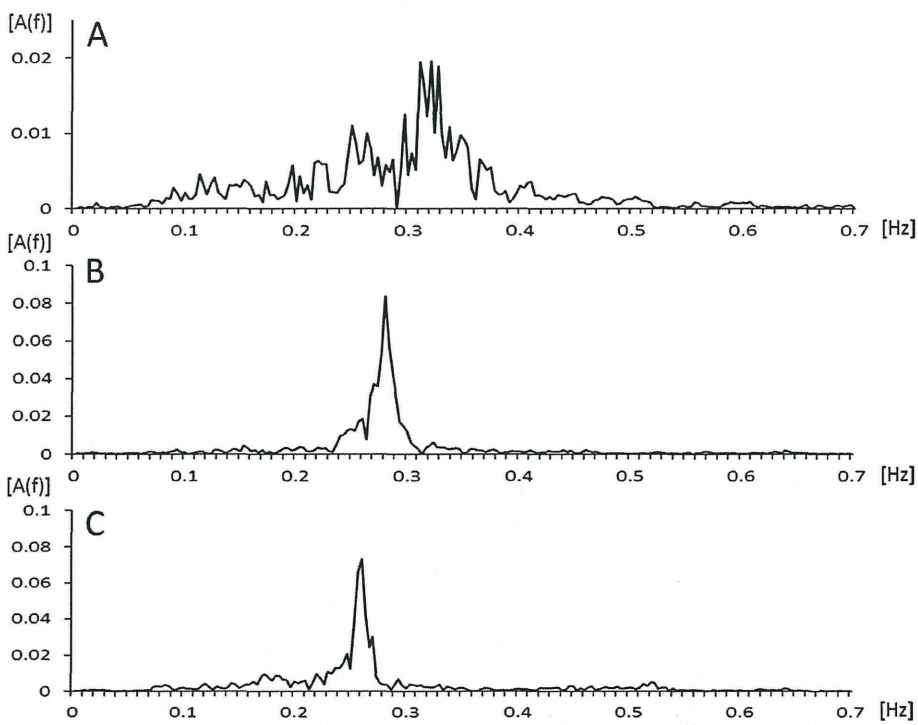

Figure 2 The typical power spectrum of a patient with DLB (A), a patient with AD (B) and a patient without dementia (C) obtained by fast Fourier transform. The amplitude spectrum of the patient with DLB is distributed over the whole displayed frequency. AD, Alzheimer's disease; A(f), amplitude spectrum; DLB, dementia with Lewy bodies.

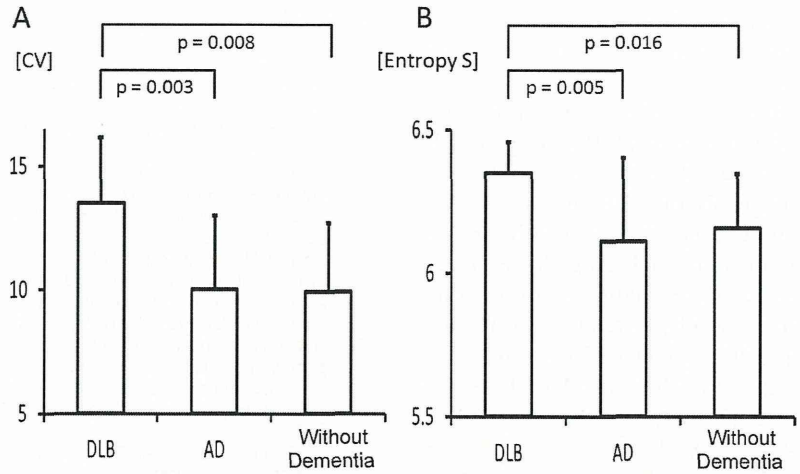

Figure 3 (A) Coefficient of variation for breath-to-breath respiratory time in patient with DLB, patient with AD and patients without dementia. One-way analysis of variance with Games-Howell post hoc tests; significant differences in DLB versus AD (p =0.003) and DLB versus without dementia (p=0.008). (B) The comparison of Shannon entropy S in DLB patients, AD patients and patients without dementia. One-way analysis of variance with Games-Howell post hoc tests; significant differences in DLB versus AD (p=0.005) and DLB versus without dementia (p=0.016). Values are mean±SD. AD, Alzheimer's disease; CV, coefficient of variation; DLB, dementia with Lewy bodies; n.s., not significant.

breath-to-breath time in patients without dementia was not significantly different from that reported in previous studies of control patients.[19 20] Although the complication with hypertension was greater in AD group than in DLB group, no significant differences were found in the measures of breathing patterns between patients with hypertension and the patients without hypertension (data not shown).

Patients with DLB exhibit many clinical features other than dementia, visual hallucinations and parkinsonism. For example, Rapid Eye Movement sleep behaviour disorder, severe autonomic dysfunctions, such as orthostatic hypotension, repeated syncope and systematised delusions, can be seen in patients with DLB.[21] Furthermore, in a previous study, we reported a high frequency of periodic limb movements in patients with DLB.[22] The results of the current study indicating that DLB patients exhibit dysrhythmic breathing compared with normal patients suggest that irregular breathing patterns may be a new clinical feature of DLB.

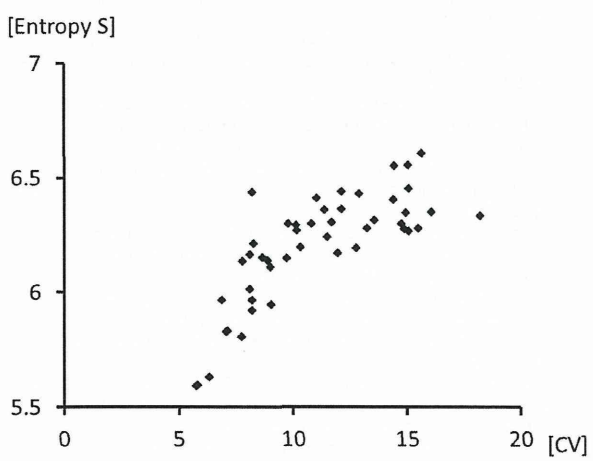

Figure 4 Scatter plot showing the relationship between the coefficient of variation for breath-to-breath respiratory time and the value of Shannon entropy S. A significant correlation (r=0.78, p<0.001) was found between the coefficient of variation (CV) and the Shannon entropy S.

Currently, DLB and AD are diagnosed according to their respective clinical diagnostic criteria,[2 6] and differentiation of these two diseases is frequently difficult. Our findings of different breathing patterns between patients with DLB and AD suggest the usefulness of the spectral analysis of breathing for discriminating patients with DLB from those with AD. Because the diagnostic threshold had a high sensitivity in our study, the spectral analysis of breathing may be useful for making an exclusive diagnosis. While the utilisation of SPECT and MIBG myocardial scintigraphy are limited to well-equipped hospitals, the spectral analysis of breathing can be performed more easily and with lower expenses. As a screening tool for the diagnosis of DLB, the spectral analysis of breathing patterns may be cost-effective and useful.

The FFT is an important tool for digital signal processing of the information commonly encoded in the sinusoids that form the signal. Additionally, the important information to be evaluated is the frequency and amplitude of the component sinusoids. To reduce spectral noise, a Hamming window is used that involves the multiplication of the signal by a smooth curve. The result is plotted graphically in terms of amplitude and frequency. In addition, we used Shannon entropy in this study to quantify the variability of the amplitude spectrum, namely breathing irregularities. This measure has been widely used in a range of biological applications in which quantitative descriptions of data regularity are

required.[23 24] The Shannon entropy indicates the degree of uncertainty and is higher when the variability of the parameter is greater.

There are several limitations to the current study. First, we included patients with possible DLB and probable DLB in the same DLB group. In addition, we did not make a pathological diagnosis of DLB or AD. A prospective investigation on the course of breathing patterns and cognitive impairment, including the eventual pathological diagnosis, should be examined in a future study. Second, no arterial blood gas analyses were performed. Therefore, a possible effect of hypercapnia or hypocapnia on breathing cannot be excluded. To evaluate more precisely, arterial blood gas analyses should be examined in a future study, as well. Third, we could not make the raters of respiratory measures completely blinded to the clinical symptoms of the patients, although the final diagnosis of dementia had been made independently, and the analysis of respiratory measures had been performed objectively according to the predetermined protocol. Finally, the number of patients in each group was relatively small. We could not rule out the contribution of other comorbid factors to irregular breathing. However, our data provide the first evidence of irregular breathing in DLB patients. In a future study, an additional investigation involving a larger number of patients should be performed.

In conclusion, we found that DLB patients exhibit dysrhythmic breathing compared with that observed in AD patients and patients without dementia. Ataxic breathing may be a new clinical feature of DLB, and the spectral analysis of breathing patterns may be clinically useful for the diagnostic differentiation of DLB from AD.

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Contributors SH was involved in design, analysis, interpretation and drafting of the article. YY was responsible for conception, design, analysis, interpretation and drafting of the article. YU-K and KI were involved in design. MT and TM were involved in analysis. MA and YO were involved in design and interpretation. All authors had full access to the data and take responsibility for its integrity and the accuracy of the analysis.

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Competing interests None.

Patient consent Obtained.

Ethics approval The study was approved by the Institutional Review Board of the Graduate School of Medicine, University of Tokyo, and written informed consent was obtained from all participants before the study.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement No additional data are available.

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Respiratory dysrhythmia in dementia with Lewy bodies: a cross-sectional study

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脳腫瘍核医学検査の現状

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はじめに

核医学検査の特徴は，体内に存在する物質やそれに近い化合物に，ガンマ線放出核種やポジトロン放出核種を標識したトレーサを極めて少量投与し，生理的条件を乱すことなく，体内物質やその体内動態に関わる生理機能を断層画像上で可視化・定量化することである[1]．目的ごとに決められたプロトコールに従って，体内に分布したトレーサから放出されるガンマ線をガンマカメラで，あるいは，ポジトロン核種から放出されたポジトロンと電子との衝突により発生する消滅放射線をPET装置で計測する．計測したカウントを，投与したトレーサの放射能濃度とcross calibrationによって関連付け，位置情報と合わせることで，投与したトレーサ分布を断層画像上で計測可能となる．これをもとにトレーサ分布を解析し，血流量や代謝量，受容体密度などの定量指標を算出し，病態の特徴を抽出する．腫瘍診療においては，腫瘍細胞の増殖に必要なグルコース代謝やアミノ酸代謝，核酸代謝量などから，腫瘍細胞の増殖能や浸潤範囲を測定・描出する．これは，術前においては腫瘍と非腫瘍性病変の鑑別や悪性度の診断に役立つ．また，悪性度は腫瘍内でも不均一であることが多く，もっとも悪性度の高い部位を同定することは生検部位の決定に重要で，正確な病理診断，悪性度判定に寄与する．治療後においては治療効果判定や再発診断に利用されている．治療前

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脳腫瘍に用いられる主な放射性薬剤

Radiotracer	Biomarker
PET	
^{18}F-FDG	Glucose metabolism (GLUT, hexokinase)
^{11}C-MET	Protein metabolism (amino acid transporter, protein synthesis)
^{18}F-FET	Protein metabolism (amino acid transporter)
^{18}F-FDOPA	Protein metabolism (amino acid transporter, amino acid decarboxylase)
^{18}F-FMISO	Hypoxia (nitroreductase, low pO_2)
^{18}F-FLT	DNA synthesis (TK-1)
SPECT	
^{201}TlCl	Potassium analogue (blood flow, Na-K ATP activity)
^{123}I-IMP	Amphetamine (cerebral blood flow, nonspecific amine-binding site)

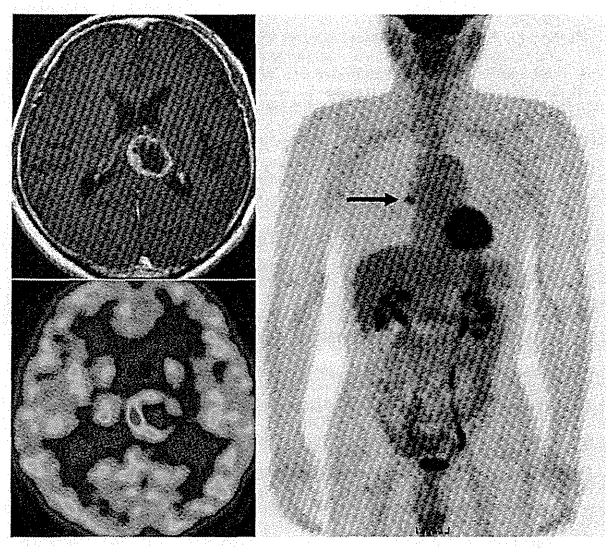

図1
造影MRIで左視床にリング状の増強効果を認める(左上段)．FDG-PETでもリング状の高集積を認めた(左下段)．全身PET撮像にて右肺門部に肺癌を検出した(矢印)．

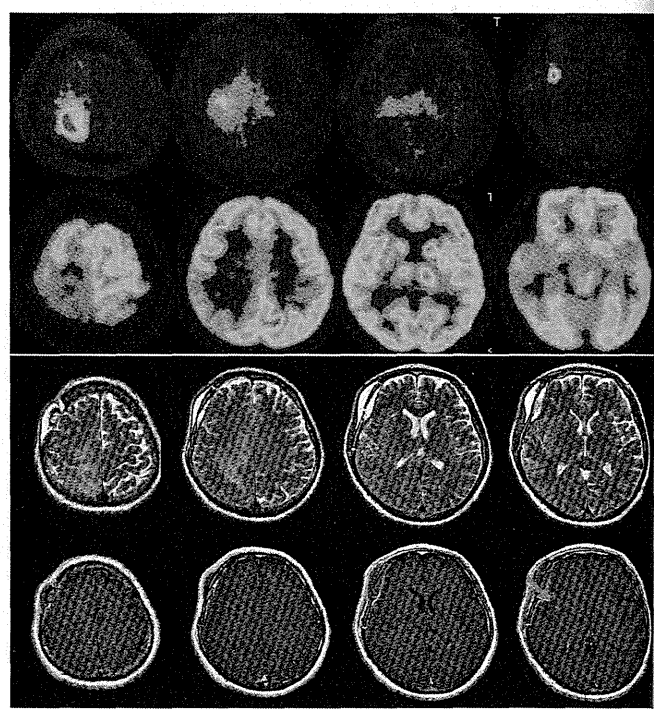

図2　上からMET-PET，FDG-PET，MRI T2WI，Gd造影T1WI
MRI上は右島回に増強効果域を認める(矢印)．MET-PETでは，右視床から右頭頂葉，左帯状回に及ぶ広い範囲で異常集積増加が検出された．

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の悪性度や腫瘍の治療反応性は予後推定にも応用されつつあり，治療開始後早期の治療反応性の評価は，個々の患者に対する治療効果の早期判断に期待されている．

放射性薬剤

脳腫瘍を対象に使用されている主なトレーサを表に示す．PET検査では，ブドウ糖類似体である2-deoxy-2[^{18}F]fluoro-D-glucose（^{18}F-FDG），アミノ酸ではL-[methyl-^{11}C]methionine（^{11}C-MET），*O*-(2-[^{18}F]fluoroethyl)-L-tyrosine（^{18}F-FET），L-3,4-dihydroxy-6-[^{18}F]fluorophenylalanine（^{18}F-FDOPA）などがあり，なかでも^{11}C-METの有用性は多く報告されている．ヌクレオシドであるチミジン誘導体としては3'-[^{18}F]fluoro-3'-deoxythymidine（^{18}F-FLT）が臨床応用されつつある．SPECT検査では^{201}Tl-chloride（TlCl）やN-isopropyl-p-[^{123}I]-iodoamphetamine（IMP）がある．一般に，SPECT検査に用いるガンマ線放出核種は半減期が6時間～数日と比較的長く，長時間の追跡が可能であり，また，臨床上使いやすいが，PET検査に使用されるポジトロン放出核種は半減期が短く（^{11}Cは20分，^{18}Fは110分），多くは，自施設のサイクロトロンを用いて核反応によってポジトロン放出核種を製造し，ホットラボ室内で合成装置を用いて薬剤合成し，品質検定・管理を行う必要がある．

FDGとメチオニン

脳腫瘍診療におけるPET検査は，現在，FDG-PETのみが保険収載されており，FDG-PETが中心となるが，FDG-PETを補うようにMET-PETの有用性も高い．一般に，FDGの集積が正常灰白質と同程度かそれより高い集積増加がある場合は，悪性度の高い腫瘍が示唆される．また，FDG-PETは軀幹部も撮像することで全身の腫瘍検索ができる．特に，転移性脳腫瘍が疑われる場合は同時に原発巣の検索が可能である．図1は，頭部に悪性を疑うリング状の異常集積増加を認め全身のPET撮像を追加したところ，右肺門部に肺癌を検出した症例である．また，FDG集積は神経シナプス活動を反映するため，病変や治療による局所脳機能低下もFDG分布に反映される．一方で，FDG-PETの欠点としては，正常灰白質のFDG集積が高いため，しばしば腫瘍範囲の同定が困難なことである．この点を克服するトレーサとして有用性が高いのはMET-PETである．METは正常灰白質へ集積は非常に少なく，腫瘍の描出に優れ，腫瘍の進展範囲の同定に役立つ．集積が周囲脳実質より高いMET集積部位は，低悪性度腫瘍を含め病変の存在が示唆される．ただし，擬陽性，擬陰性も報告されつつあり，脱髄疾患などの炎症性疾患や血腫の周囲，虚血部位など反応性組織はMET集積が周囲より高くなることがある．Oligodendrogliomaやjuvenile pilocytic astrocytomaはWHO Grade Ⅱに分類されているが，他のgliomaのGrade Ⅲ相当にMETの集積が高いことが多い．Gliomatosis cerebriではFDG，METともに陽性に描出されないことがあり注意が必要である．

FDGやMETの集積程度の評価方法は視覚的評価のほか，半定量的指標としてL/N比（lesion/normal ratio）が広く用いられている．これは正常灰白質を参照領域としたときの評価法で，正常灰白質（normal）と病変部位（lesion）に関心領域（ROI：region of interest）を設定し，それぞれのカウント平均の比で算出されることが多い．L/N比は，撮像装置や撮像プロトコール，ROIの設定部位によって異なるが，おおむねFDG-PETではL/N比0.8以上，METでは2.0以上であると高悪性度腫瘍の可能性が高い[2]．また，低悪性度腫瘍の描出にはMET-PETが有用で，Herholzらは，MET-PETのカットオフ値をL/N比1.47とした場合[3]，腫瘍性病変と非腫瘍性病変との鑑別において検出感度76%，特異度87%であったと報告している．

FDGやMETなどのPET薬剤がMRIやCTの造影剤と大きく異なるのは，血液脳関門（BBB）の破綻に依存せず病変部に到達し，腫瘍細胞に取り込まれることである．特に神経膠腫はBBBを破壊せずに浸潤性に増殖する特徴があるため，造影MRI，CTでは描出されない浸潤範囲もPET上は描出される．この性質は，治療後，すでにBBBが破綻している部位の治療効果判定や，再発診断にも有用である．

再発診断においても，FDG，METともに異常集積増加を認めれば腫瘍残存や再発が疑われ，集積程度は細胞増殖能や予後など腫瘍悪性度と相関する．もともと低悪性度腫瘍で再発時，FDG集積が正常灰白質より高い場合は悪性転化が考慮される．一方，神経膠芽腫の再発であっても，治療後変化を伴うため集積がごく軽度のこともあり，経時的変化をみるなど注意が必要である．転移性脳腫瘍の場合は，腎細胞癌や腺癌など組織型によっては集積が低いことがある．このため，再発診断における集積程度のカットオフ値を決めるのは難しいが，神経膠腫（初回病理診断Grade Ⅱ～Ⅳ）30例を対象とした再発診断時のPET研究では，FDGのL/N比0.8，METのL/N比2.0～2.2以上の症例は予後不良であったと報告されている[4]．放射線治療後の再発と放射線壊死との鑑別についてMET-PETの研究では，放射線治療終了後17ヵ月以降の77症例を対象に，神経膠腫ではL/N比1.58，転移性脳腫瘍ではL/N比1.41とした場合，それぞれ感度・特異度は75～79%であったとの報告がある[5]．

神経膠芽腫の症例のMET-PET，FDG-PET画像を図2に呈示する．MET-PETでは腫瘍細胞の進展範囲がFDG-PETより明瞭に描出され，MRI上のT2WI高信号域やGd増強効果部位よりも広範囲である．FDG-PETではMETの異常集積増加部位に対応し，白質領域では異常集積増加が認められるが，灰白質では周囲正常灰白質よりも低く描出されている．

その他のPETイメージング

MET以外のアミノ酸イメージングとして比較的多く研