CORRELATION OF VENTRICULAR ASYMMETRY WITH METABOLIC ASYMMETRY IN FRONTOTEMPORAL DEMENTIA


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SUMMARY

Background and Purpose: The clinical presentation of frontotemporal dementia (FTD) is often asymmetrical in terms of both its clinical features and atrophy on MRI. Asymmetry in the lateral ventricle size on structural neuroimaging in FTD patients may have clinical significance. However, this has not been systematically investigated yet. This study compares the ventricular asymmetry seen on MRI with that of the asymmetric glucose metabolism using FDG-PET in patients with FTD.

Methods: Nineteen FTD patients who underwent both brain MRI and FDG-PET were retrospectively selected. As control groups, 23 and 11 age and sex-matched healthy normal subjects underwent either brain MRI or FDG-PET, respectively. The ventricular asymmetry index (VAI) was obtained in two ways: by visual rating (VAI-V) and by measuring the lateral ventricular volumes (VAI-ROI). The hemispheric asymmetry of the glucose metabolism on FDG-PET (MAI) was assessed in three ways: 1) by visual rating (MAI-V), 2) by counting the FDG activity of each hemisphere on normalized and smoothed PET images (MAI-ROI) and 3) by counting the number of voxels with significant hypometabolism based on statistical parametric mapping results (MAI-SPM).

Results: The VAIs on MRI (VAI-V and VAI-ROI) were highly correlated, as were the MAIs (MAI-V, MAI-ROI, and MAI-SPM) on FDG-PET. More importantly, the VAIs on MRI and the MAIs on FDG-PET showed high correlation.

Conclusions: Ventricular asymmetry in FTD patients was common (78.9%) and there was a high correlation between the ventricular structural asymmetry and the hemispheric metabolic asymmetry. Therefore, it would be reasonable to interpret that the hemisphere with larger ventricle on MRI in FTD patients is undergoing a more active degenerative process.

Key words: dementia, frontotemporal, Magnetic Resonance (MR), Positron emission tomography (PET), Brain, atrophy, Brain, MR, Brain, PET.

INTRODUCTION

Degenerative disorders causing dementia usually involve both hemispheres, resulting in diffuse and symmetrical brain atrophy. However, it has also been reported that asymmetric degeneration between hemispheres often exists in degenerative dementias. Corticobasal degeneration is one of the representative diseases that cause asymmetric degeneration [2] and even in Alzheimer’s disease asymmetric degeneration has been reported [6, 9]. These asymmetric structural or functional degenerations are known to be correlated with the clinical findings.

Frontotemporal lobar degeneration (FTLD) comprises a group of degenerative dementias that show clinical characteristics associated with frontal
or temporal lobe lesions. It is probably the second most frequent cause of presenile degenerative dementia. FTLD includes three distinct clinical syndromes: frontotemporal dementia (FTD), progressive non-fluent aphasia (PA) and semantic dementia (SD) [22]. Degenerative processes in FTLD are more likely to be focal, circumscribed or asymmetric compared to Alzheimer’s disease [3, 15, 29]. Patients with PA present with language disturbance and have asymmetric atrophy in the dominant frontal area [22]. Patients with SD have circumscribed atrophy in the anterior temporal lobe, which is predominant in the left hemisphere in most cases [22]. Previous reports have suggested that the clinical presentation and hemispheric degeneration of FTD is also often asymmetrical [3, 4, 17, 19, 21, 29, 31]. However, most of these studies investigated the hemispheric asymmetry on either the functional or structural images only, and correlation between these has rarely been performed. Some studies divided the FTD patients into left or right hemisphere impaired groups by visual inspection of the FDG-PET [1] or SPECT [3, 22, 28]. Other studies quantified the functional changes by the ROI method [5], but obtained no asymmetry indices. The studies measuring asymmetric brain atrophy on MRI [16, 17] carried out no correlation analysis with the functional changes. To our knowledge, only two studies [22, 28] have compared the structural and functional images, but the comparisons were only made by visual inspection. Most of these studies included patients with PA and SD, which are known to preferentially affect the dominant hemisphere.

Several methods have been proposed for assessing the hemispheric atrophy on MRI or CT. These include visual inspection (dilated ventricle in the presence of increased sulcal size in the ipsilateral hemisphere), ventricular brain ratio [30] or voxel-based morphometry [23]. Of these, measurement of the dilated lateral ventricle would be the most practical way to assess asymmetric brain atrophy. Asymmetric hemispheric atrophy usually results in asymmetric dilatation of the lateral ventricle. Thus, asymmetry in the lateral ventricle size on structural neuroimaging in FTD patients may have clinical significance. The comparison of visual rating and quantitative measurement of ventricular asymmetry has been carried out in AD [1] but not in FTD. This asymmetry, however, is difficult to interpret because even normal subjects have asymmetric lateral ventricles [26]. The aim of current study was to assess the significance of the ventricular asymmetry in FTD patients by comparing the ventricular asymmetry on MRI with the metabolic changes on 18F-fluoro-2-deoxy-d-glucose positron emission tomography (FDG-PET) scans. Also, we extend the comparison of visual rating and quantitative measurement of the ventricular asymmetry to FTD patients.

MATERIALS AND METHODS

Subjects

Of 55 consecutive FTD patients diagnosed at Samsung Memory Disorder Clinic in the past 7 years, 19 who underwent both MRI and FDG-PET were recruited. Another 26 patients were excluded as they had undergone brain CT, or either FDG-PET or brain MRI, but not both. The remaining ten patients had FTD combined with motor neuron disease and were excluded. All patients fulfilled the consensus criteria for FTD [22]. None had evidence of a stroke, head trauma or hydrocephalus, by history and MRI.

As control groups, 23 sex- and age-matched healthy volunteers for MRI comparison (NC-MRI) and another 11 sex- and age-matched healthy volunteers for FDG-PET comparison (NC-PET) were also recruited. All subjects from both control groups were right-handed as assessed by Edinburgh Handedness Inventory. Their cognitive function as screened by Mini-Mental State Examination was normal and all the subjects also had no history of neurological and psychiatric illnesses or specific abnormalities on neurological and neuropsychological examinations. The detailed demographic features for the patients and control groups are presented in Table I.

Measurement of ventricular asymmetry on brain MRI

Brain MRIs were obtained using a Genesis Signa (1.5T, GE Medical Systems, Milwaukee, WI). All images were transferred into a picture archiving and communicating system (PACS; GE PACS). In six of 19 patients, the MRI images were taken at other hospitals. These images were scanned into the same PACS system, and analyzed in the same way. Axial MR scans from all the hospitals were obtained with a slice thickness of 7 mm.

Table I. – Demographic features of subjects.

<table>
<thead>
<tr>
<th></th>
<th>FTD</th>
<th>NC-MRI</th>
<th>NC-PET</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number</td>
<td>19</td>
<td>23</td>
<td>11</td>
</tr>
<tr>
<td>Age</td>
<td>53.8±9.5</td>
<td>57.2±10.8</td>
<td>62.2±5.7</td>
</tr>
<tr>
<td>Disease duration</td>
<td>2.8±1.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>9/10</td>
<td>8/15</td>
<td>4/7</td>
</tr>
<tr>
<td>Mean MMSE score</td>
<td>17.1±8.1</td>
<td>29.1±1.0*</td>
<td>29.1±1.1*</td>
</tr>
</tbody>
</table>

*p < 0.001.
To evaluate the ventricular asymmetry in FTD, two methods were used. First, the ventricular asymmetry was assessed by visual inspection. With T1-weighted MR images from 19 FTD and 23 NC-MRI groups randomly presented, two neurologists, blinded to the clinical information, rated the ventricular asymmetry on a five-point scale (−2, −1, 0, 1, and 2). Ratings of −2 and +2 represented moderately larger left or right lateral ventricle compared to the contralateral side, respectively; −1 and +1 mildly larger left or right lateral ventricle compared to the contralateral side, respectively; and 0 little difference between the two lateral ventricles. Mean values of the two raters were used as the ventricular asymmetry index of the visual rating (VAI-V).

Second, the volumes of the lateral ventricle in the patients and controls were measured by outlining the ventricular boundary using a manual pixel-wise method, with the aid of PACS workstation, on T1-weighted MRI. All areas of the visible lateral ventricles in the axial cuts were summed and multiplied by the slice thickness (7 mm). The ventricular asymmetry index of these ROI measurements (VAI-ROI) was computed by the following formula [21, 30]:

$$\text{VAI-ROI} = \frac{\text{Volume of right ventricle} - \text{Volume of left ventricle}}{\text{Volume of right ventricle} + \text{Volume of left ventricle}} \times 200$$ and ranged from −200 to 200; negative values indicated the left ventricle was larger than the right, positive values indicated the opposite. The ventricular volume was measured independently by two neurologists blinded to the clinical information. The final VAI-ROI was defined as an average of the two rater’s measurements.

### PET imaging

PET scans were acquired for 30 min, starting 40 min after an intravenous injection of 4.8 MBq/kg FDG, using a GE Advance PET scanner. The in-plane and axial resolutions of the scanner were 4.9 and 3.9 mm full-width at half maximum, respectively. Subjects fasted for at least 4 h before the PET scans were obtained. The PET images were reconstructed using a Hanning filter (cut-off frequency = 4.5 mm), and displayed in 128×128 matrices (pixel size = 1.95×1.95 mm with a slice thickness of 4.25 mm). Attenuation correction was performed with a uniform attenuation coefficient (μ = 0.096 cm⁻¹).

### SPM analysis of regional glucose metabolism

Prior to statistical analysis, using SPM99 (Wellcome Department of Cognitive Neurology, Institute of Neurology, London, UK) [23] implanted in a Matlab 5.3 environment (MathWorks Inc., Sherborn, MA), all the images were preprocessed for spatial normalization into the MNI (Montreal Neurological Institute) template to remove inter-subject anatomical variability, then smoothed with a FWHM 16 mm Gaussian kernel to increase the signal-to-noise ratio and account for the subtle variations in the anatomical structures. The count of each voxel was normalized to the average count of the cerebellum using a customized program, as the cerebellum is known to be one of the least affected regions in FTD [1, 12, 26, 33]. The images of the FTD patients were compared with those of NC-PET subjects in a voxel-wise manner, using SPM99 for individual analyses (p<0.001 uncorrected, extent threshold k=200).

To visualize the t-score statistics (SPM{t} map), the significant voxels were projected onto the 3D rendered brain, or a standard high-resolution MRI template, provided by SPM99, thus allowing anatomic identification.

### Analysis of hemispheric asymmetry of glucose metabolism

To evaluate the hemispheric asymmetry of the glucose metabolism in FTD, three methods were employed. First, the hemispheric asymmetry of the glucose metabolism was assessed by visual inspection. Two neurologists, blinded to the clinical information, rated the hemispheric asymmetry on a five-point scale (−2, −1, 0, 1, and 2) with the FDG-PET images from the randomly presented 19 FTD and 11 NC-PET subjects. Ratings of −2 and +2 represented moderate hypometabolism in the left or right hemispheres, compared to the contralateral side, respectively; −1 and +1 mild hypometabolism in the left or right hemispheres, respectively, compared to the contralateral side; and 0 little difference between the hemispheres. The mean values of the two raters were used as the metabolic asymmetry index of the visual method (MAI-V).

Second, the AIs of the metabolisms between the hemispheres were obtained using ROI analyses of the FDG PET images in each of the FTD patients (MAI-ROI). From the preprocessed PET images with the cerebellar normalization (mean FDG activity of cerebellum = 50) described above, two ROIs were defined: one for the right cerebral hemisphere and the right side of cerebellum (right ROI) and brain stem and the other for the left side of the brain.
(left ROI). In each ROI, the total FDG activity was counted, and an AI between the hemispheres was computed using the following equation: \( \text{MAI-ROI} = \frac{\text{average FDG activity of the left ROI} - \text{average FDG activity of the right ROI}}{\text{average FDG activity of the right ROI}} \times 200 \).

Third, the AI was also calculated by the SPM method (MAI-SPM). On the SPM(t) map of each patient, the number of voxels with significant \((P < 0.001\) uncorrected) hypometabolism, compared with the healthy control group, were counted in each hemisphere, and an AI between the hemispheres was calculated using the following equation: \( \text{MAI-SPM} = \frac{\text{No. of hypometabolic voxels in the right hemisphere} - \text{No. of hypometabolic voxels in the left hemisphere}}{\text{No. of hypometabolic voxels in the left hemisphere} - \text{No. of hypometabolic voxels in the right hemisphere}} \times 200 \). Positive MAI-ROI and MAI-SPM values indicated that the right hemisphere was more hypometabolic (in terms of extent and/or intensity) than the left; negative values indicated the opposite.

**Statistical Analysis**

Data were expressed as the mean ± SD. Differences between visual rating data were analyzed by Mann-Whitney test and other data were by \( t \) tests. The correlation of visual rating and ventricle measurement between two persons and the correlation between each AI were evaluated by calculating the Spearman coefficient. For continuous variables (VAI-V and MAI-V), weighted kappa coefficients were calculated. With the exception of the SPM analyses, a \( p \) value of 0.05 was considered significant.

**RESULTS**

Illustrations of ventricular asymmetry measurement are presented in figure 1 along with corresponding metabolic asymmetry measurement.

**Volume of lateral ventricle on MRI**

The inter-rater agreement in the measurement of the ventricle volume was excellent \((r=0.907, p<0.001)\). The mean lateral ventricle volumes of the normal controls \((N=23)\) were 14,520.2 ± 6934.1 and 15,844.7 ± 7,977.3 mm\(^3\) for the right and left ventricles, respectively.

The mean lateral ventricle volume of the FTD patients \((N=19)\) were 28,249.0 ± 10,991.2 and 33,109.7 ± 14,025.5 mm\(^3\) for the right and left ventricles, respectively. The total ventricle volumes of the FTD patients were about twice those of the normal controls \((p<0.001)\).

**Ventricular asymmetry on MRI**

In the NC-MRI group, the mean volume of left the lateral ventricle was larger than that of the right by 9.1%. Eighteen of the 23 normal subjects (78.3%) had larger left than right ventricles. As in the controls, the volume of left ventricles of the FTD patients was larger than the right by 17.2%. Thirteen of 19 patients (68.4%) had larger left than right ventricles.

The distribution of visual rating (VAI-V) and ROI method (VAI-ROI) of the ventricular asymmetry is illustrated in figure 2. The correlations for VAI-V and VAI-ROI were high \((r=0.730, p<0.001\) for visual rating; \(r=0.907, p<0.001\) for ROI method). From the Spearman correlation, the correlation coefficient for both the VAI-V and VAI-ROI was 0.883 \((p<0.001)\), indicating that the visual rating of the ventricle asymmetry on MRI correlated highly with the actual measurements.

To compare the degree of asymmetry, the absolute AI values from the patient and control groups were compared. The absolute values of VAI-V of the FTD group \((0.4±0.8)\) were greater than those of the NC-MRI group \((0.3±0.5)\) \((p=0.006)\) and those of the VAI-ROI of the FTD group \((24.±15.0)\) were also greater than those of the NC-MRI group \((17.2±14.1)\), but this did not reach statistical significance \((p=0.121)\).

The FTD patients were considered to have asymmetric lateral ventricles if their VAI-ROI was beyond the 95% confidence interval \((95% \text{ CI}; −17.6 \sim 0.4)\) of the NC-MRI group. According to this criterion, 15 of the 19 FTD patients (78.9%) had asymmetric lateral ventricles. Of these 15 patients, 10 had larger left than right ventricles (left group, VAI-ROI less than 95%CI, -17.6); five patients had larger right than left ventricles (right group, VAI-ROI more than 95%CI, 0.4).

**Metabolic asymmetry on PET**

In the visual rating of the PET, the inter-rater correlation was excellent \((r=0.957, p<0.001)\). The distribution of MAI-V, MAI-ROI, and MAI-SPM is illustrated in figure 2. The absolute values of MAI-V of the FTD \((1.4±0.7, N=19)\) were greater than those of the NC-PET group \((0.0±0.0, N=11)\) \((p<0.001)\). Twelve of the 19 patients had negative MAI-V, i.e., predominant hypometabolism in the left hemisphere; five had positive MAI-V, i.e., predominant hypometabolism in the right hemisphere; the remaining two had symmetrical hypometabolism.

When the metabolic asymmetry was analyzed by the ROI method, the absolute MAI-ROI of the FTD \((8.4±5.3)\) was greater than that of the NC-PET group \((2.7±1.1)\) \((p=0.002)\). When the asymmetric hypometabolism was defined as a MAI-ROI beyond the 95% confidence interval \((95% \text{ CI}; −3.4 \sim −1.9)\) of the NC-PET group, 18 of the 19 FTD patients (94.7%) had asymmetric hypometabolism. Ten of these 18 belonged to the left group, as their MAI-ROIs were less than 95% of the CI \((-3.4); eight belonged to the right group, as their MAI-ROIs were more than 95% of the CI \((-1.9); the remaining one patient had symmetric hypometabolism.

When the metabolic asymmetry was analyzed by the SPM method, 11 of the 19 patients had positive MAI-S values, indicating that hypometabolism was more severe in the left hemisphere than the right,
and the remaining 8 patients showed the opposite pattern.

The MAI-V correlated highly with the MAI-ROI ($r=0.806, p<0.001$), and with the MAI-SPM also ($r=0.742, p<0.001$). MAI-ROI and MAI-SPM also showed high correlation ($r=0.888, p<0.001$).

**Comparison of ventricular asymmetry with metabolic asymmetry**

The comparison of the ventricular asymmetry on MRI and the metabolic asymmetry on FDG-PET was illustrated in **figure 1**. The correlation coefficient of the VAI-V and MAI-V was 0.789 ($p<0.001$), indicating that the visual rating of the ventricle asymmetry of the MRI correlated highly with that of the metabolic asymmetry on FDG-PET. The VAI-V correlated highly with the MAI-ROI ($r=0.620, p=0.005$), and also with the MAI-SPM ($r=0.626, p=0.004$).

Ventricular asymmetry by measuring (VAI-ROI) also showed high correlation with the metabolic asymmetry. The correlation coefficient of VAI-ROI with MAI-V, MAI-ROI and MAI-SPM were 0.782 ($p<0.001$), 0.672 ($p=0.002$) and 0.747 ($p=0.001$) respectively.

**DISCUSSION**

In our study, the mean volume of the lateral ventricles on the MRI of the normal controls were
about 15.8 and about 14.5 ml for the left and right ventricles, respectively. The left ventricle was larger than the right, replicating the results of previous studies [5]. Previous studies measured the ventricle volumes by ventricular casts [17], pneumoencephalography [31], CT [10] or MR images [5]. The lateral ventricular volumes of the normal subjects in these studies were generally smaller than ours. This volume discrepancy is thought be associated with the differences in age (our subjects were older).

Measurement of the ventricular asymmetry on MRI showed that the absolute values of both the VAI-V and VAI-ROI of the patient group were greater than those of the controls. Also, 15 of the 19 FTD patients had VAI-ROI beyond the 95% CI of the NC-MRI group. These findings indicate that asymmetric hemispheric atrophy is common in FTD. Also, hemispheric metabolic asymmetry was found to be common and intense in FTD, even after the patients with PA and SD had been excluded.

There were more patients with atrophy or hypometabolism in the left than the right hemisphere. The reason for this over-representation of the left-impaired group is not known. One possible explanation is that FTD, in nature, may preferentially affect the left hemisphere. A pathological study has demonstrated that there are greater left- than right-sided atrophic changes in most cases of FTD [11]. An MRI study has also shown more atrophy on the left side [3], although the opposite pattern has been reported in another study [8]. Another possible reason for the over-representation of the left-impaired group may be related to sampling bias. Left-dominant patients can show language disturbances, even in the early stages. Thus, it is more likely that those patients are brought to neurology clinics. On the other hand, right-dominant patients may present predominantly with behavioral or psychiatric abnormalities, being brought to psychiatric clinics first, or misdiagnosed as having psychiatric illnesses other than FTD.
In this study, the ventricular asymmetry on structural images (MRI) were measured and correlated with the hemispheric metabolic asymmetry on the functional images (FDG-PET) in FTD patients. Although only one (VAI-ROI) of the two visual ratings of ventricular asymmetry failed to differentiate normal from pathological ventricular asymmetry, the asymmetry indices of FTD patients from the structural imaging correlated highly with those of the functional images. Therefore, it would be legitimate to interpret that the hemisphere with the larger ventricle on MRI in FTD patients is undergoing a more active degenerative process. These results are in agreement with those of previous studies that have investigated the ventricular asymmetry in other dementias [6, 27, 32]. Furthermore, measurement of the ventricular asymmetry in FTD patients by gross visual inspection showed good correlation with the actual measurement of the ventricular volume by the outlining method and metabolic asymmetric indices on PET, indicating that the visual rating of ventricular asymmetry is valid.

Our study has limitations. Although normal controls for MRI and PET groups had no abnormalities in neurological evaluation, we did not obtain the past history of perinal injury that might affect the ventricular asymmetry. Also, the controls for MRI and PET groups differed. Thus, the correlation between ventricular asymmetry and metabolic asymmetry could not have been investigated in controls. In our study, as mentioned earlier, there was an overlap in the results of visual rating (VAI-ROI) of ventricular asymmetry between demented and control populations, which was not the case with visual ratings (MAI-V and MAI-ROI) of metabolic asymmetry. The reason for this discrepancy is unknown but it can also be attributed to the fact that we did not set the single control group for MRI and PET analysis. Alternatively, even if there is ventricular asymmetry in normal population, it may not implicate metabolic asymmetry.

RÉFÉRENCES


Les urgences en pathologie ORL et maxillo-faciale de la clinique à l’image de l’image au traitement
K. Marsot-Dupuch, S. Bobin
2e édition revue et corrigée, Sauramps médical 2005 (426 pages)


Kathlyn Marsot-Dupuch et Serge Bobin se sont entourés de spécialistes de très haute notoriété pour offrir aux lecteurs une revue exhaustive, actuelle, pratique et richement illustrée. Cet ouvrage est indispensable à tout spécialiste amené à prendre en charge les urgences ORL.

Radiologic-pathologic correlations. From the head to toe
N.C. Gourtsoyiannis, P.R. Ros
Edition Understanding the Manifestations of disease, Springer-Verlag-Heidelberg 2005 (797 pages)

Avoir accès à un livre confrontant les données de l’anatomie pathologique à celle de l’imagerie médicale est le souhait de la grande majorité des praticiens. Nicholas C. Gourtsoyiannis et Pablo R. Ros ont réuni des spécialistes de grande notoriété pour rédiger un ouvrage clair, didactique et très informatif. Ce livre comporte sept chapitres consacrés aux pathologies du système nerveux, ORL, thoracique, abominable et gastro-intestinale, uro-génitale, musculaire et articulaire et mammaire. Les affections les plus habituellement rencontrées sont étudiées à la fois sous l’angle anatomique grâce à une description à la fois macroscopique, microscopique et radiologique en faisant référence à la modalité d’imagerie la plus appropriée.

Cette double approche offre aux lecteurs toutes les données nécessaires à une meilleure compréhension de l’image. Ce livre se doit d’être retrouvé dans toutes les bibliothèques d’imagerie et proposé à tout spécialiste pour qui l’imagerie est une étape indispensable de la prise en charge des patients tant il est remarquable par sa clarté et l’excellence de son iconographie.