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Original Article

Half of the patients with amyotrophic lateral sclerosis after ventilation have apparent frontotemporal lobar atrophy: A quantitative survey of 92 patients by CT imaging

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Short running title

Frontotemporal lobar atrophy in ALS

Abstract

Background: A significant clinicopathologic and genetic overlap has been suggested between amyotrophic lateral sclerosis (ALS) and frontotemporal lobar degeneration (FTLD).

Aim: To determine the overlap, we assessed the cerebral atrophy as a surrogate indicator of FTLD in ALS inpatients with post-tracheostomy positive pressure ventilation by CT imaging analysis.

Methods: The extent of cerebral atrophy was quantitatively evaluated in 92 ALS patients (age: 68.3 ± 11.0 ys and disease duration: 7.6 ± 4.8 ys) and 42 age-matched healthy controls (age: 60.4 ± 13.6 ys) by computer-mediated assessments of sizes of the following four areas [anterior temporal (TL) and frontal lobes (FL) and inferior (IH) and anterior horn (AH) of the lateral ventricle] and of the corresponding intracranial fossae, to minimize individual head-size differences.

Results: More than half of the ALS patients clearly exhibited the parenchymal atrophy in TL and FL regions and the ventricular dilatation in IH and AH areas, both of which exceeds the age-associated physiological changes. By clustering analysis using degrees of TL and FL atrophy and of IH and AH dilatation, the ALS patients examined were grouped into 5 clusters resulting in the following characteristics: 1) normal to mild frontotemporal cortical atrophy (51%); 2) mild frontotemporal lobar atrophy (FTLA) (26%); 3) moderate FTLA (15%); 4) severe FTLA (4%); and 5) severe temporal lobar atrophy (3%).

Conclusion: Half of the ALS patients after ventilation had apparent frontotemporal lobar atrophy by CT imaging, and such patients would develop FTLD.

Key words:

Aging and dementia, Brain CT imaging, Frontotemporal lobar degeneration, Motor neuron disease, Tracheostomy positive pressure ventilation

Introduction

It is now evident that patients with amyotrophic lateral sclerosis (ALS) have variable lesions not only in upper and lower motor neurons, but also in other areas of the brain, especially those involving cognitive functions^{1,2}. The clinicopathological association of ALS with dementia was demonstrated in a portion of ALS patients decades ago³ and was classified as ALS-D. In individuals having presenile dementia with motor neuron disease, abnormal ubiquitin-positive intracytoplasmic inclusions were often found in neurons in their extra-motor cortices⁴. TAR-DNA-binding protein of 43 kD (TDP-43) was subsequently identified as a major component of those ubiquitin-positive inclusions and proved to be a disease-related protein in ALS and frontotemporal lobar degeneration with ubiquitin-positive inclusions (FTLD-U)^{5,6}. The current concept is thus that ALS, ALS-D and FTLD-U are included in a broad spectrum of clinicopathological multisystem disease, called TDP-43 proteinopathy^{1,7-9}. Recent epidemiological analysis of a large cohort of ALS patients has revealed the association of ALS with cognitive impairments and to lesser extent frontotemporal dementia¹⁰. However, there are no available data of dementia based on imaging analysis in ALS patients¹¹.

Our Setagaya Neurological Hospital has accepted many ALS patients for long-term medical care and as a notable unique feature, all patients when admitted have already been on tracheostomy positive pressure ventilation (TPPV) installed by other hospitals. In Japan, installation of TPPV in ALS patients is much higher than that in other countries¹² and there are many neuropathological¹³⁻¹⁶ and neuroradiological¹⁷ reports concerning ALS-D. In this regard, usage of TPPV allows for long-term survival of ALS patients beyond respiratory failure and some of them enter into severely impaired communication manifestations characteristic of a “totally locked-in state”, in which they are in complete palsy of all motor systems including the eyes¹⁸.

Given the aforementioned concept of the clinicopathological spectrum and the clinical observation of ALS patients under long-term TPPV in our hospital, we hypothesized that the ALS patients would develop the frontotemporal dementia (FTD) as the consequence of the increased disease duration under TPPV even though no signs of dementia were shown at the beginning of motor symptoms. Taking advantage of our hospital where many ALS patients have been stable in physical condition under TPPV

for a long time and CT scan analysis can be performed on such severe patients at intervals with less suffering than MRI, we have quantitatively evaluated the long-term changes of cerebral atrophy in ALS patients through analysis of conventional brain CT, instead of MRI, images as a surrogate indicator of FTLD. This present paper describes the results of such evaluation.

Patients and Methods

Patients. Ninety-two patients (53 males, 39 females) diagnosed as ALS according to the revised El Escorial diagnostic criteria¹⁹ at other hospitals were admitted to Setagaya Neurological Hospital and consecutively enrolled in this study from March 2010 to December 2011. All patients were under TPPV at the admission and thereafter. When we examined all available medical information, dementia was not verified in any cases either before or at the time when motor symptoms emerged. A single case of familial ALS affecting two brothers was found to have a mutation in the superoxide dismutase 1 gene. Among 92 enrolled patients, including bulbar type 25, spinal type 62, and others 5 patients in accordance with the site of onset, the mean \pm standard deviation (SD) of the disease onset age was 60.7 ± 12.3 y (range of 29-82 y); the current age (age at our last CT examination) was 68.3 ± 11.0 y (41-87 y); the disease duration was 7.6 ± 4.8 y (1-30 y); the duration from the disease onset to the TPPV installation was 2.7 ± 2.4 y (0-14 y); the duration after the TPPV installation was 4.9 ± 3.7 y (0-19 y). For controls, 42 age-matched healthy participants (21 males, 21 females) were enrolled and the current age (age at CT examination) was 60.4 ± 13.6 y (40-85y). This study was approved by the ethics committee of Setagaya Neurological Hospital (#2010-01) and written informed consent was obtained from all participants, mostly from their substitutes, before enrollment in the study in accordance with the Declaration of Helsinki.

Methods. Brain CT scans were conducted using GE ProSpeed II. To quantitatively evaluate the frontotemporal lobar atrophy, we selected two axial slices of CT images²⁰ (thickness of 1 mm). One where the area of tip of the inferior horn (IH) of the lateral ventricle was maximal, was selected for assessment of the degree of atrophy in anterior temporal lobe (TL) and dilatation of IH (**Fig. 1a**). The other where the area of anterior horn (AH) of the lateral ventricle was maximal, was chosen for assessment of the degree of atrophy in frontal lobe (FL) and dilatation of AH (**Fig. 1b**). To minimize individual head-size differences, the ratio of a given parenchymal area to the corresponding intracranial area was calculated as the relative size, called an index of each region²¹⁻²³. Namely, in slice a, the trapezoid area surrounded by the lines of the

anterior and posterior margins and the lateral curves of the bilateral middle cranial fossae was first defined as the area of the middle cranial fossae (see Fig. 1a). Areas of TL (A), IH (B) and middle cranial fossae (C) in bilateral sides within the trapezoid were then estimated by computer, and the ratio of A/C and B/C were respectively calculated as the TL and IH indices for their relative sizes. In slice b, the semicircular area surrounded by the line adjacent to the posterior margins of the bilateral AH, crossing at the right angle to the mid-sagittal line and the lateral curves of the bilateral anterior cranial fossae was defined as the area of the anterior cranial fossae (see Fig. 1b). Area of FL (D), AH (E) and anterior cranial fossae (F) in both sides within the semicircle were then measured, and the ratios of D/F and E/F were respectively calculated as the FL and AH indices for their relative sizes. ImageJ, Java-based image processing program, was used for tracing the CT images and calculating the areas.

Data analysis. Parenchymal indices of TL and FL and ventricular indices of IH and AH in both ALS patients and age-matched healthy controls were plotted against their current age (ys) on the same plane. The correlation coefficients and regression lines in each group were calculated. ANCOVA was used to evaluate the index differences between patients and controls. A p value of < 0.05 was defined as statistically significant. In order to express the degree of brain atrophy in ALS patients relative to controls, two lines parallel to the control regression line were drawn at the point of ± 2 SDs from the control predicted index (see Fig. 2). If the parenchymal index of ALS patients was equal to the (predicted $- 2$ SDs) index of age-matched controls, then the degree of atrophy was scored as 1 unit. If the ventricular index of ALS patients was equal to the (predicted $+ 2$ SDs) index of age-matched controls, the degree of dilatation was scored as 1 unit. Degree 'n' of atrophy or dilatation of ALS patients respectively corresponded to the (predicted $- 2n$ SDs) or (predicted $+ 2n$ SDs) index of age-matched controls, and degree '0' of atrophy or dilatation was equal to the control predicted index (see Fig. 3). Four sets of data of ALS patients, *i.e.*, degrees of the TL and FL atrophy and of the IH and AH dilatation, were subjected to non-hierarchical k -means cluster analysis.

Results

Comparison of brain parenchymal and ventricular indices between ALS patients and age-matched healthy controls. To quantitatively evaluate the cerebral mass changes in individuals with different head size, we assessed the ratio of the size of a given parenchymal or ventricular area to the size of the corresponding intracranial region as

an index of its relative size. The parenchymal indices in the anterior temporal (TL) and frontal (FL) lobes as well as the ventricular indices in the inferior (IH) and anterior (AH) horns among 92 ALS patients (open circles) as well as 42 age-matched controls (filled circles) were plotted on the same plane against their current ages (ys). The correlation coefficients and regression lines of these indices in each group, ALS (green lines) and controls (red lines), were calculated. Red dotted lines parallel to the control regression lines corresponded to the control indices of (predicted value \pm 2 SDs) (**Fig. 2**).

Anterior temporal lobe (TL): Negative correlation was evident between TL indices and current ages in both patient and control groups (**Fig. 2a**), suggesting a reduction in the relative TL size as a function of age in both groups. The regression line of each group was significantly distinct each other ($p < 0.01$). The control one was $Y = -0.0010X + 0.564$ (X: current age and Y: predicted TL index) with a correlation coefficient of $r = 0.42$ ($p < 0.01$), whereas the patient one was $Y = -0.0016X + 0.520$, with a correlation coefficient of $r = 0.31$ ($p < 0.003$). This suggested that the reduction in relative TL size was slightly faster in ALS patients than in controls. The incidence of ALS patients with TL index outside 2 SDs of the control predicted values was 58/92 (63%).

Inferior horn (IH): Positive correlation was recognized between IH indices and current ages in both groups (**Fig. 2b**), suggesting an increase in the relative IH size as a function of age in both groups and coincident with the reduction of relative TL size on the same plane of middle cranial fossae. Regression lines of both groups were significantly different ($p < 0.05$). The control one was $Y = 0.000046X - 0.0007$ (X: current age and Y: predicted IH index) with a correlation coefficient of $r = 0.29$ ($p = 0.065$), whereas the patient one was $Y = 0.00070X - 0.0297$, with a correlation coefficient of $r = 0.37$ ($p < 0.0002$), suggesting that the increase in relative IH size was much faster in ALS patients than in controls. The incidence of ALS patients with IH index outside 2 SDs of the control predicted values was 55/92 (60%).

Frontal lobe (FL): Negative correlation was recognized between FL indices and current ages in both groups (**Fig. 2c**), suggesting the age-associated reduction of relative FL size in both groups. Their regression lines were significantly different ($p < 0.05$). The control one was $Y = -0.0019X + 0.997$ (X: current age and Y: predicted FL index) with a correlation coefficient of $r = 0.57$ ($p < 0.01$), whereas the patient one was $Y = -0.0027X + 0.885$, with a correlation coefficient of $r = 0.29$ ($p < 0.006$), suggesting the slightly faster decrease of relative FL size in ALS patients compared to controls. The incidence of ALS patients with FL index outside 2 SDs of the control predicted values was 74/92 (80%).

Anterior horn (AH): Positive correlation was observed between AH indices and current age in both groups (**Fig. 2d**), suggesting the age-associated increase in relative AH size in both groups, coincident with the reduction of relative FL size on the same plane of anterior cranial fossae. Regression lines of the two groups appeared to be different but not statistically significant ($p = 0.06$). The control one was $Y = 0.0010X - 0.0064$ (X : current age and Y : predicted AH index) with a correlation coefficient of $r = 0.67$ ($p < 0.01$), whereas the patient one was $Y = 0.0015X + 0.0079$, with a correlation coefficient of $r = 0.35$ ($p < 0.0006$), suggesting the slightly faster increase of relative AH size in ALS patients compared to controls. The incidence of ALS patients with AH index outside 2 SDs of the control predicted values was 48/92 (52%).

Cluster analysis in ALS patients. Based on the above indices of four regions (TL, FL, IH and AH) in both ALS patients and controls along with their statistical analysis data, we re-plotted the patient indices according to their extents of distance from the control predicted indices. If a given patient's parenchymal index is equal to the 'predicted' or 'predicted - 2 SDs' index of the age-matched control, then it is respectively scored as '0' or '1' unit as a degree of atrophy. If a given patient's ventricular index is equal to the 'predicted + 2 SDs' index of the age-matched control, it is scored as '1' unit as a degree of dilatation. In **Fig. 3**, units of TL (**a**), IH (**b**), FL (**c**) and AH (**d**) among 92 ALS patients were plotted against their current ages (ys). [The explanation of different colors is described in the following section.] It was clearly demonstrated that significant fractions of ALS patients had more than 1 unit degree of atrophy in FL and TL regions as well as of dilatation in IH and AH regions, suggesting that the brain atrophy observed in ALS patients exceeds the age-associated, physiological atrophy. Notably, the trend in parenchymal atrophy in ALS patients was roughly similar in TL and FL regions albeit slightly more in FL. The degree of ventricular dilatation in ALS patients was more obviously deviated in IH than AH. Among 92 ALS patients, the mean atrophy unit (± 1 SD) was 1.44 (± 0.93) for TL and 1.87 (± 1.15) for FL and the mean dilatation unit (± 1 SD) was 3.32 (± 4.63) for IH and 1.17 (± 1.08) for AH.

To explore any relatedness or commonality among these 92 ALS patients examined, the non-hierarchical k -means cluster analysis was employed using four sets of unit values (atrophy unit of TL and FL and dilatation unit of IH and AH). In brief, ALS patients were clustered by "n" in a way that maximizes the separation of those clusters while minimizing intra-cluster distances relative to the cluster's mean. Many of these algorithms repeatedly assigned patients to different numbers of clusters while searching for some optimal separation or informative outcome. When ALS patients were divided

into 5 clusters, we found the following interesting aspects (**Table 1** and **Fig. 4**). Each cluster was numbered according to the size of patient population: cluster 1 to 5 respectively contained 47 (51%), 24 (26%), 14 (15%), 4 (4%) and 3 (3%) patients. Remarkably in this clustering, the degrees (units) of both TL atrophy and IH dilatation advanced as the cluster number increased, except for cluster 5. Similar trend was also observed with the degrees of AH dilatation and FL atrophy, although the FL atrophy was slightly more prominent in cluster 2 than cluster 3. When these cluster designations with different colors were incorporated into the Fig. 3 (atrophy/dilatation *versus* current age), the dilatation degree of IH had the clearest inter-cluster separation. Both the current age and the onset age were roughly increased and the duration (yr) to TPPV installation was decreased as the cluster number advanced, albeit slight inversion between clusters 3 and 4 (**Table 2**). Both current and onset ages and duration to TPPV installation were significantly different between clusters 1 and 3. There was no trend between the disease duration and the cluster. CT images of a representative panel of patients of each cluster were shown in **Fig. 5**. TL atrophic lesions accompanied with IH dilatation were more evident as cluster numbers advanced (upper panel). Similar trend was also observed with AH dilatation and FL atrophy in Cluster 1 to 4 (lower panel).

Discussion

The Setagaya Neurological Hospital has accepted many ALS patients after ventilation for long-term care. Therefore, the ultimate goal of our study is to clarify the extent of complication of dementia during the long clinical course of a neuro-degenerative disease, ALS after ventilation. Because our ALS patients had been under TPPV at admission, it was often difficult to accurately evaluate their cognitive functions by conventional communication-based tests. Therefore, we did not evaluate the cognitive functions *per se* at bedside, but instead, employed a conventional brain CT imaging analysis to quantitatively assess the TL and FL parenchymal atrophy and the IH and AH ventricular dilatation as indication of dementia.

To evaluate atrophy-associated cerebral changes by CT imaging, we selected four regions, *i.e.*, anterior temporal lobe (TL) around the temporal pole, frontal lobe (FL), inferior horn (IH) of lateral ventricle in para-hippocampal area, and anterior horn (AH) of lateral ventricle. With two selected slices (one showing maximal tip of IH and the other showing maximal AH)²⁰, brain atrophy was quantitatively evaluated by calculating the ratios of the above parenchymal and ventricular regions to the corresponding intracranial areas to minimize individual head-size differences. This CT image-based assessment was performed for 92 ALS patients consecutively admitted to

our hospital as well as for 42 age-matched healthy individuals and these ratios were used as indices of brain atrophy and ventricular dilatation. To our knowledge, this report has first described the results from large quantitative survey of CT image-based alterations in frontotemporal regions of ALS patients after ventilation.

CT image-based, TL and FL atrophy and IH and AH ventricular dilatation became evident as the age advanced in both ALS patients and controls, but significantly much profound in patients than controls, except for AH. More than half the patients were outside the range of 2 SDs of the control predicted indices of TL and FL atrophy and IH and AH ventricular dilatation: 63% for TL, 60% for IH, 80% for FL, and 52% for AH. Since the index values varied depending on the selected regions, the indices were thus converted to units 'n' as defined by '2n SDs' distant from the corresponding predicted values. These units could thus be used as relative degrees of brain atrophy and ventricular dilatation in those areas. Results from non-hierarchical *k*-means cluster analysis of 92 ALS patients using these units provided an informative grouping into five clusters. When clusters 1 to 5 were numbered according to the size of patients population (n = 47, 24, 14, 4, and 3, respectively), a remarkable trend was revealed. Namely, the degree of TL and FL atrophy and IH and AH ventricular dilatation advanced as the cluster number increased, except for cluster 5. Based on these degree of atrophy and dilatation in affected areas, cluster 1 was classified as normal to 'mild' frontotemporal 'cortical' atrophy, and clusters 2 to 4 were classified as 'mild', 'moderate' and 'severe' frontotemporal lobar atrophy (FTLA), respectively. Cluster 5 was unique in that TL atrophy and IH dilatation were severe, but FL atrophy and AH dilatation were mild, thereby classified as 'severe temporal lobar' atrophy. Separation of cluster 5 might reflect the fact that temporal pole and para-hippocampal areas are known as the main pathological regions in cerebral extra-motor cortices of ALS-D^{13,14}. In addition, as the cluster number increased, trends of mean age increase in both current age and onset age and mean decrease in duration to TPPV installation were observed, but not in disease duration (see Table 2), suggesting that degrees of FTLA in ALS patients partially depend on disease onset age, *i.e.*, the younger onset, the milder progress of atrophy, including more cluster 1 patients.

In the present study we have established a CT-image based quantitative assessment of brain atrophy in 92 ALS patients under TPPV and 42 age-matched healthy controls. Our results strongly indicate that the extent of atrophy in frontotemporal region of ALS patients significantly exceeds that of the controls and such patients will likely develop frontotemporal dementia. Through the cluster analysis of the degree of atrophy or dilatation of the 4 regions in ALS patients after ventilation, half of them were found to

have apparent FTLA (clusters 2 to 5) by CT imaging, and these patients would develop FTLD.

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Figure legends

Figure 1. *Measurement of radiological areas.* In slice (a), where the area of tip of inferior horn (IH) of the lateral ventricle was maximal, we defined the trapezoid area surrounded by the lines of anterior and posterior margins and lateral curves of the bilateral middle cranial fossae as the area of the bilateral middle cranial fossae. The following radiological areas in the trapezoid were measured: area of bilateral anterior temporal lobes (TLs; **A**), area of bilateral IHs of the lateral ventricle (**B**), and area of bilateral middle cranial fossae (**C**). In slice (b), where the area of anterior horn (AH) of the lateral ventricle was maximal, we defined the semicircular area surrounded by the line adjacent to the posterior margins of the bilateral AHs, crossing at the right angle to the mid-sagittal line, and the lateral curves of the bilateral anterior cranial fossae, as the area of the bilateral anterior cranial fossae. The following radiological areas in the semicircle were measured: area of bilateral frontal lobes (FLs; **D**), area of bilateral AHs of the lateral ventricles (**E**), and area of bilateral anterior cranial fossae (**F**).

Figure 2. *Brain parenchymal and ventricular indices in ALS patients and controls.* The parenchymal indices in anterior temporal (TL; **a**) and frontal lobes (FL; **c**), and the ventricular indices in inferior (IH; **b**) and anterior horns (AH; **d**) from ALS patients (○) and controls (●) were plotted against their current ages (ys), along with the regression line of ALS patients (green) and controls (red). Red dotted lines corresponded to the ± 2 SDs of the control predicted values.

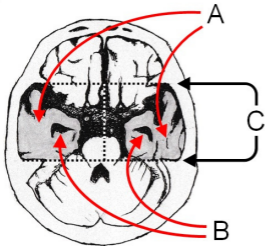
Figure 3. *Degrees of parenchymal atrophy and ventricular dilatation in ALS patients along with five different clustering.* ALS patients' indices in Fig. 2 were re-plotted according to their extents of distance from the predicted control indices as degrees (units) of atrophy or dilatation against their current ages (ys). Degrees of atrophy in anterior temporal (TL; **a**) and frontal lobes (FL; **c**) and degrees of ventricular dilatation in inferior (IH; **b**) and anterior horns (AH; **d**). Different colors indicate clusters 1 (white), 2 (red), 3 (yellow), 4 (green), and 5 (black). Dotted lines indicate ± 1 degree (unit) and correspond to the ± 2 SDs of the control predicted values.

Figure 4. *Cluster analysis of ALS patients.* The non-hierarchical *k*-means cluster analysis using degrees of atrophy/dilatation in 92 ALS patients revealed five different groups with maximum separation. Clusters were numbered according to the size of patient population. Clusters 1 to 5 contain 47 (51%), 24 (26%), 14 (15%), 4 (4%), and 3

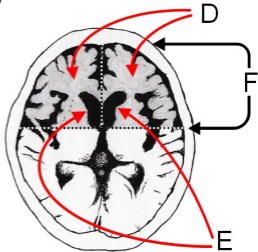
(3%), respectively, along with the indicated color code **(b)**. Degrees of atrophy or dilatation in the indicated regions of each cluster were shown as histograms with each color code **(a)**.

Figure 5. *Representative CT image of each ALS cluster.* The upper row shows anterior temporal lobe (TL) and inferior horn (IH) of the lateral ventricle, and the lower row shows frontal lobe (FL) and anterior horn (AH) of the lateral ventricle. Clusters 1 to 5 correspond **(a)** to **(e)**, respectively.

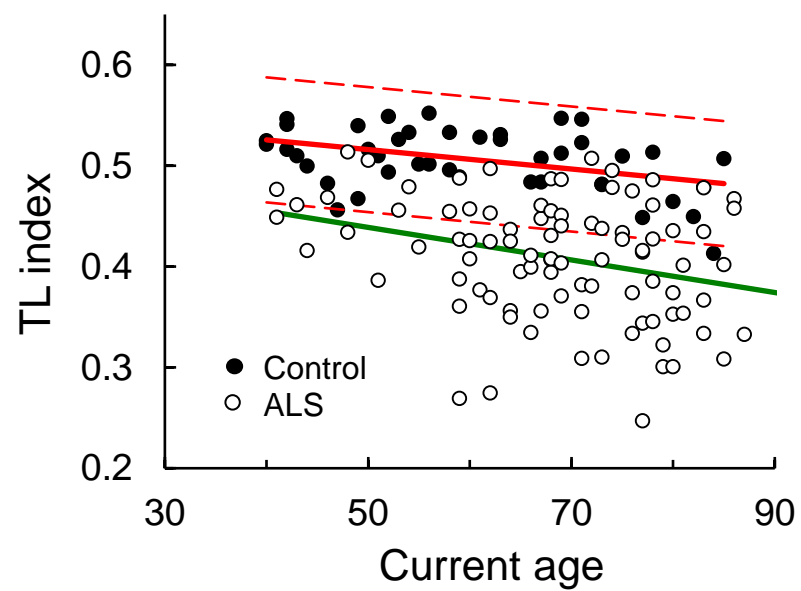
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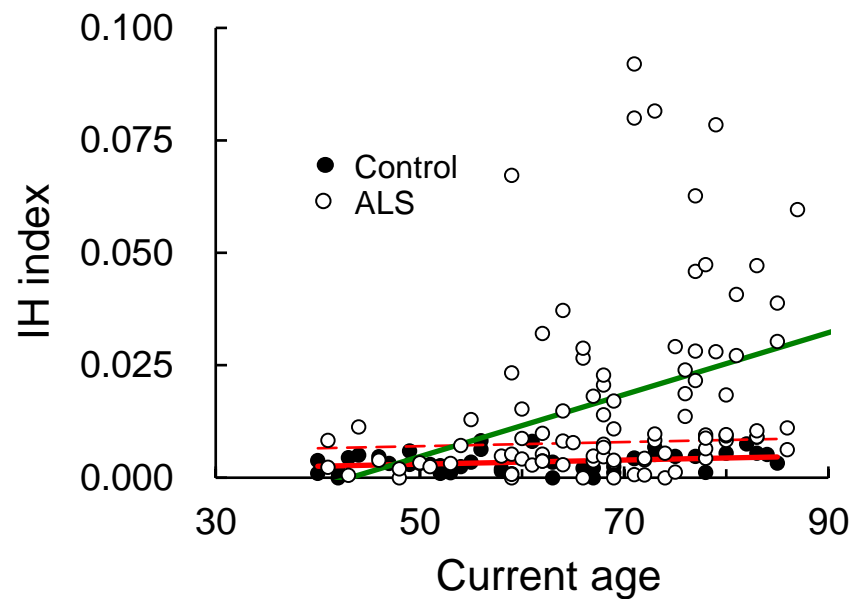
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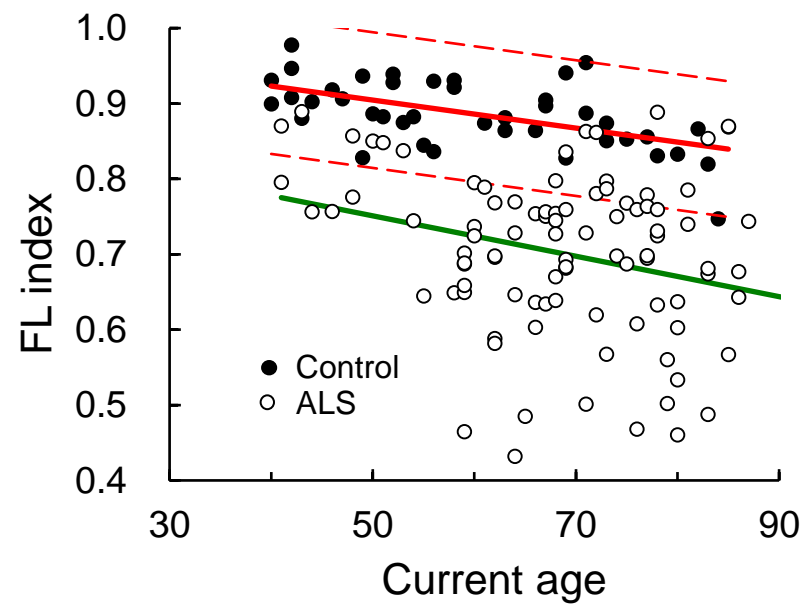
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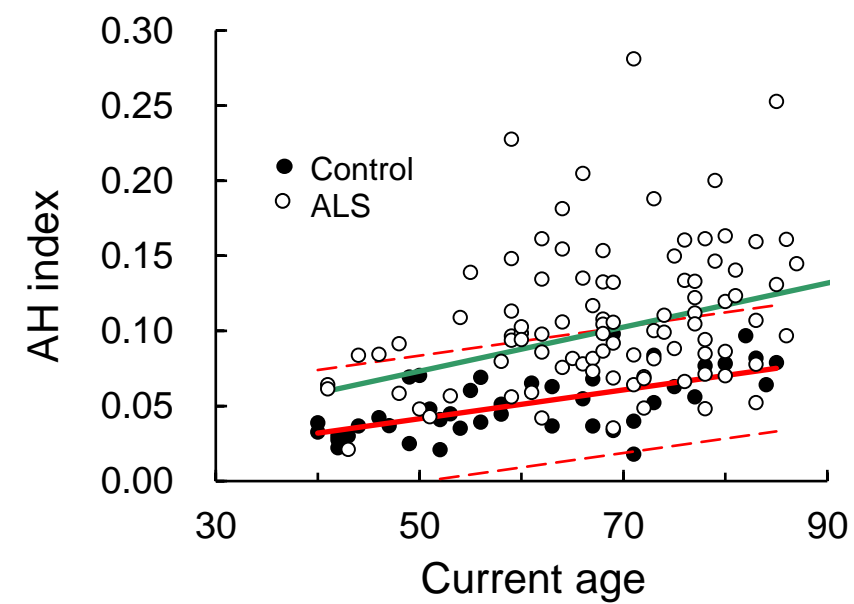
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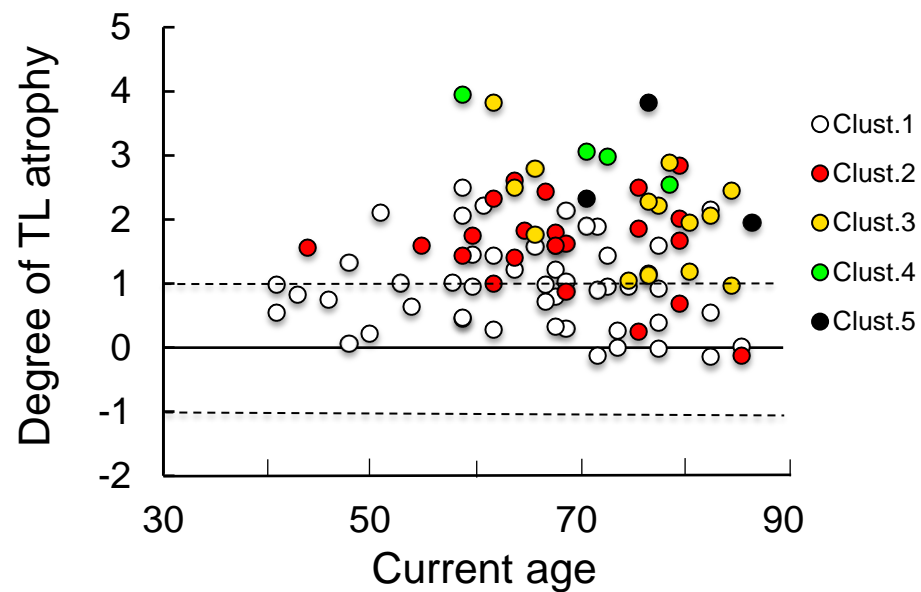
(c)



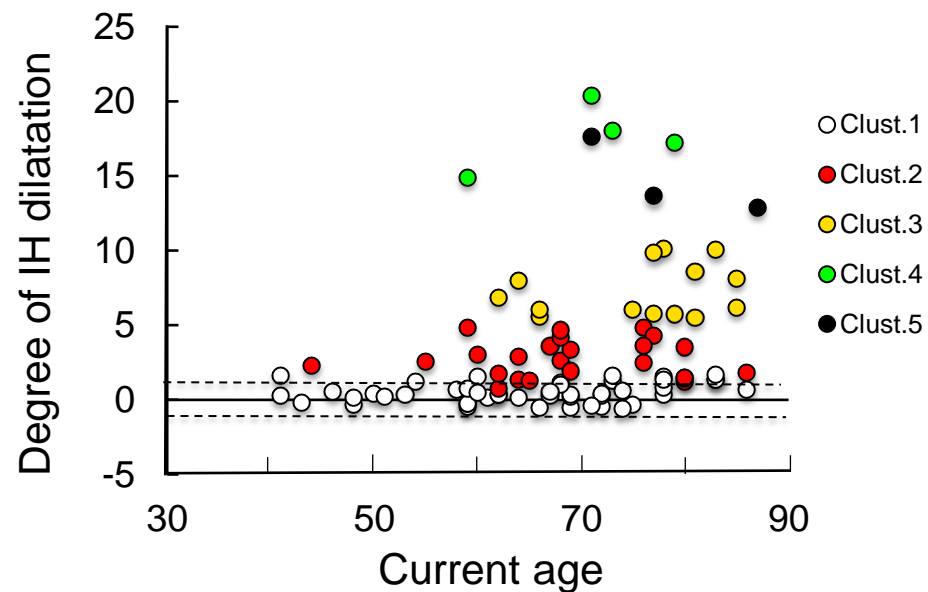
(d)



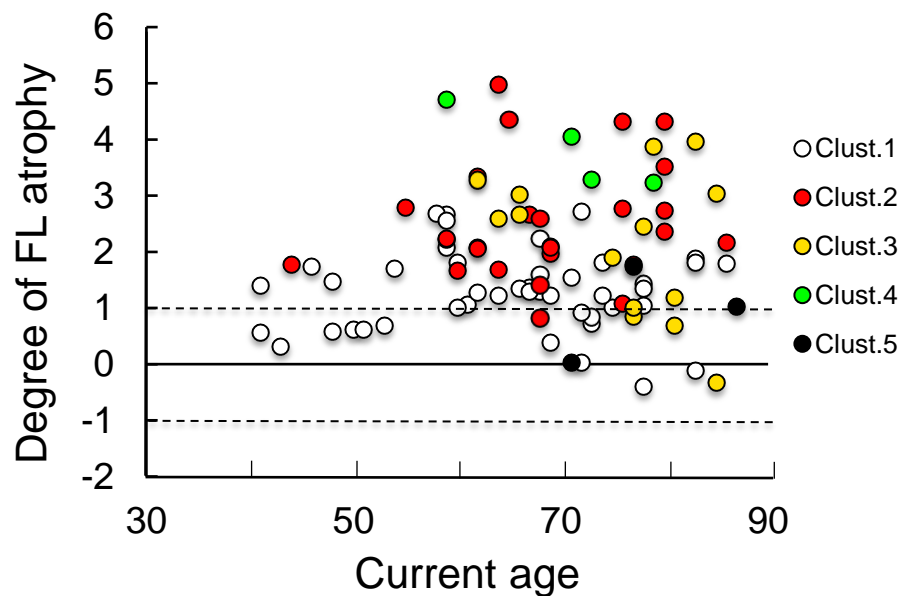
(a)



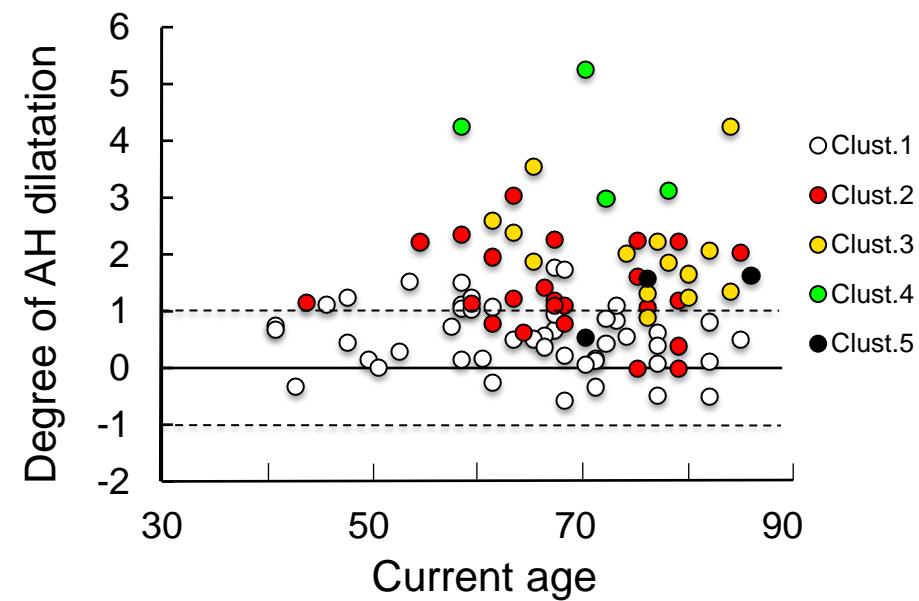
(b)



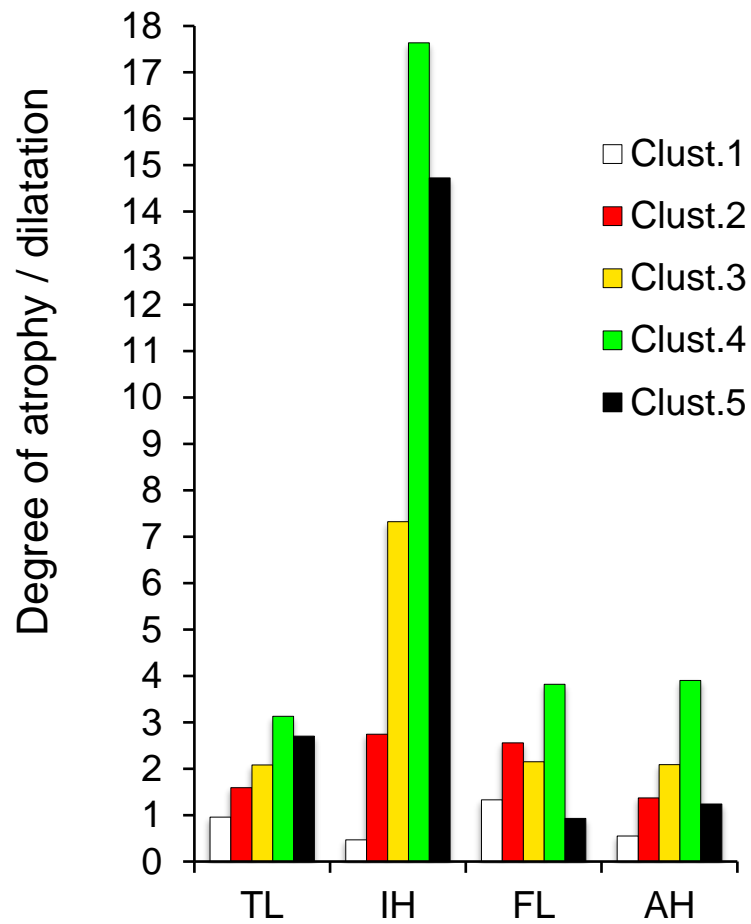
(c)



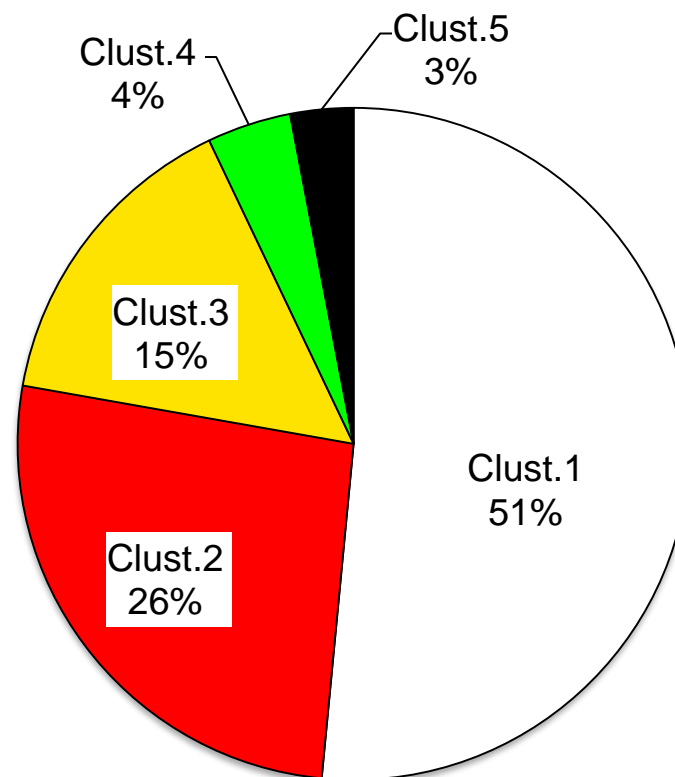
(d)



(a)



(b)



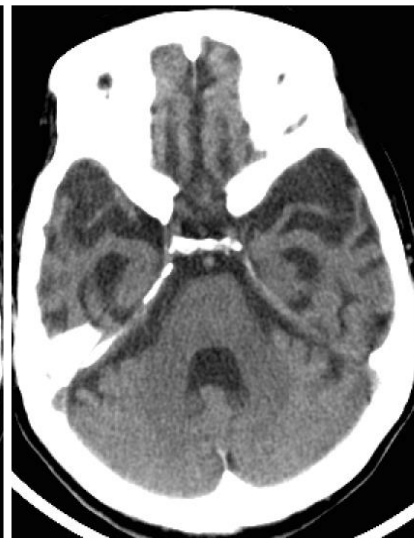
(a)



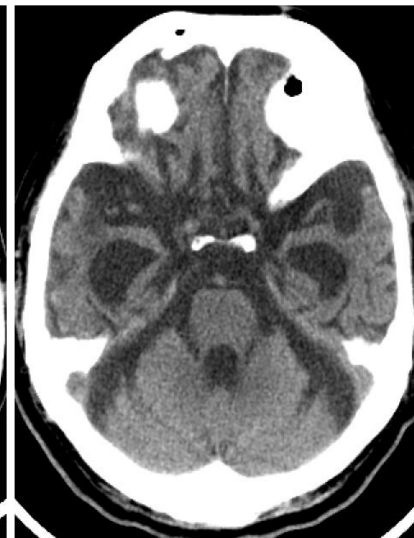
(b)



(c)



(d)



(e)

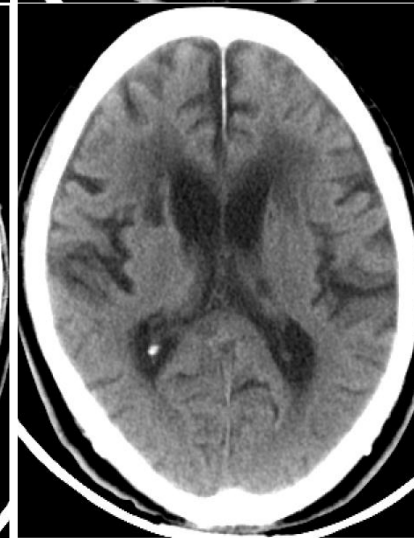
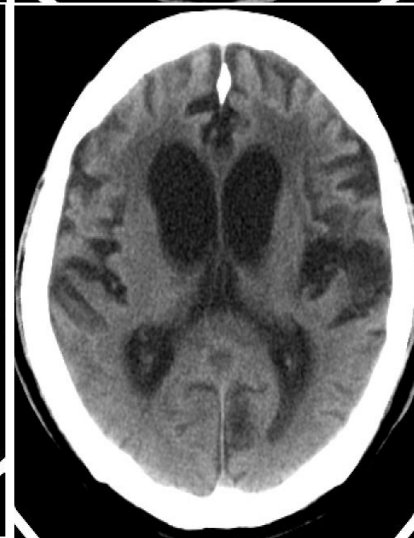
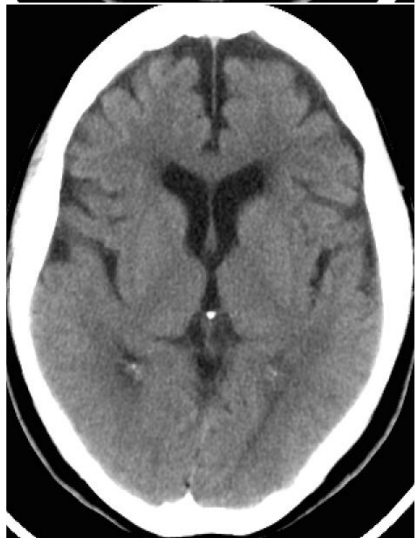


Table 1 Degree of atrophy/dilatation of 4 regions in 5 clusters of ALS patients

	n (%)	TL	IH	FL	AH
Cluster 1	47 (51)	0.96	0.47	1.33	0.55
Cluster 2	24 (26)	1.59	2.74	2.56	1.37
Cluster 3	14 (15)	2.08	7.32	2.15	2.09
Cluster 4	4 (4)	3.13	17.64	3.82	3.90
Cluster 5	3 (3)	2.70	14.73	0.93	1.24

n: number of ALS patients in each cluster

TL: Degree of atrophy of anterior temporal lobe (TL)

IH: Degree of dilatation of inferior horn (IH) of the lateral ventricle

FL: Degree of atrophy of frontal lobe (FL)

AH: Degree of dilatation of anterior horn (AH) of the lateral ventricle

Table 2 Current age, Onset age, Disease duration, and Duration to TPPV installation (mean \pm SD, ys) in 5 clusters of ALS patients

	n (%)	Current age	Onset age	Disease duration	Duration to TPPV
Cluster 1	47 (51)	64.9 \pm 11.7*	57.1 \pm 12.8*	7.8 \pm 5.4	3.4 \pm 2.7*
Cluster 2	24 (26)	69.0 \pm 9.7	60.5 \pm 10.8	8.0 \pm 5.1	2.3 \pm 2.2
Cluster 3	14 (15)	75.4 \pm 7.9*	69.1 \pm 9.3*	6.6 \pm 2.7	1.4 \pm 0.9*
Cluster 4	4 (4)	70.5 \pm 8.4	62.3 \pm 7.5	8.1 \pm 1.2	2.5 \pm 0.9
Cluster 5	3 (3)	78.3 \pm 8.1	73.7 \pm 7.4	4.8 \pm 1.6	1.1 \pm 0.9

n: number of ALS patients in each cluster

* $p < 0.05$ (difference between Cluster 1 and Cluster 3 on Current age, Onset age, and Duration to TPPV installation, respectively)