

# Chapter 8

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## Frontotemporal Lobar Degeneration

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## History

Frontotemporal lobar degeneration (FTLD), with Pick's disease as the prototype, is a progressive non-Alzheimer's disease often with the presenile onset and is characterized by degeneration and loss of neurons mainly in the frontal and temporal lobes, causing marked behavioral abnormalities, psychiatric symptoms, and language impairment, while various degrees of motor disorders may emerge during the course of disease. The concept, name, and classification of FTLD have changed over the years, and terms such as frontal lobe degeneration of non-Alzheimer type and frontal lobe dementia were once used in the past.

## Clinical classification

The term FTLD is used in cases with a definitive pathological and genetic diagnosis, while frontotemporal dementia (FTD) is used in cases with a clinical diagnosis. The term FTLD is adopted as the disease name in designated intractable diseases in Japan. In this guideline, FTLD is used and also includes clinically diagnosed cases.

FTLD is classified clinically into three types: behavioral variant frontotemporal dementia (bvFTD) with mainly prefrontal atrophy; semantic dementia (SD) with localized atrophy mainly in the temporal pole and middle/inferior temporal gyrus; and progressive non-fluent aphasia (PNFA), which is left-dominant and shows localized atrophy around the fissure of Sylvius. Refer to CQ2-6 for the classification by type of aphasia.

Also, parkinsonism and motor neuron symptoms may be observed in patients with FTLD during the course of disease. The disease type showing motor neuron symptoms is called frontotemporal dementia with motor neuron disease (FTD-MND).

## Pathological classification

Pathologically, specific proteins aggregate and deposit as inclusion bodies in neurons and glial cells. Tau protein, TAR DNA-binding protein of 43 kD (TDP-43), and fused in sarcoma (FUS) protein have been identified as the main components of the inclusion bodies<sup>1)</sup>.

Tau protein is one of the microtubule-binding proteins and is broadly classified by the number of repeats in the microtubular binding region at the C-terminal side into three-repeat tau protein and four-repeat tau protein. Tauopathy is a general term for diseases in which abnormal accumulation of phosphorylated tau protein is considered to be an essential pathogenic mechanism. The subgroup of FTLD that exhibits tauopathy is called FTLD-tau. FTLD-tau comprises cases showing accumulation of mainly three-repeat tau protein (Pick disease) and those showing accumulation of mainly four-repeat tau protein. Corticobasal degeneration, progressive supranuclear palsy, and argyrophilic grain dementia are broadly interpreted as four-repeat tauopathy with FTLD.

TDP-43 protein and FUS protein exist mainly in the nucleus, and both possess diverse functions such as transcription, splicing, RNA transport, and stabilization. In FTLD, both TDP-43 protein and FUS protein disappear from the nucleus and are observed as extracellular aggregates, and these disease types are called FTLD-TDP and FTLD-FUS, respectively. See CQ1-8 for a detailed description of pathology.

## Relationship between clinical classification and pathological classification

It has been reported that more than half of bvFTD cases are FTLD-TDP type, while approximately 70% of PNFA cases are FTLD-tau type (PSP, CBD, Pick disease), and approximately 80% of SD are FTLD-TDP type<sup>2)</sup>.

## Diagnosis

For diagnostic criteria, see CQ8-1.

## Family history

Family history is evident in 30 to 50% of the cases in European and American countries but is almost absent in Japan. In familial cases, mutations have been identified in several genes, including the *tau* gene, the *TARDBP* gene, the *FUS* gene, and the *progranulin* gene. Abnormal expansion of a hexanucleotide repeat in intron 1 of the *C9orf72* gene is the most frequent cause in European and American countries, but very rarely in Japan.

## Treatment

FTLD is a progressive degenerative disease, and curative treatment that can modify the natural course has not been developed. When patients show motor neuron symptoms, pay special attention to the onset of respiratory failure and dysphagia. Parkinsonism and repeated falls may be observed, but levodopa preparations have limited use or are often ineffective.

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## What are the diagnostic key points and diagnostic criteria for frontotemporal lobar degeneration (FTLD)?

### Answer

Among various types of frontotemporal lobar degeneration (FTLD), the criteria developed by the International Behavioral Variant Frontotemporal Dementia Criteria Consortium (FTDC) in 2011 are recommended for the diagnosis of behavioral variant frontotemporal dementia (bvFTD). For semantic dementia (SD), the use of the clinical diagnostic characteristics for semantic dementia proposed in 1998 is recommended, with additional reference to the clinical diagnostic features for semantic variant progressive aphasia proposed in 2011. B

### Comments and evidence

FTLD is classified clinically into behavioral variant frontotemporal dementia (bvFTD), semantic dementia (SD), and progressive non-fluent aphasia (PNFA). Among them, bvFTD and SD are included as designated intractable diseases in Japan.

#### 1. Diagnostic criteria for bvFTD

The FTDC diagnostic criteria reported by Rascovsky et al.<sup>1)</sup> are used. The sensitivity of the FTDC criteria is 93% for possible bvFTD and 80% for probable bvFTD, and the positive predictive value of cases diagnosed as possible bvFTD is 90%<sup>2)</sup>. Harris et al.<sup>3)</sup> studied mainly early-onset cases and reported high reliability, with 95% sensitivity and 82% specificity for possible bvFTD, and 85% sensitivity and 95% specificity for probable bvFTD.

The major false-positive cases are Alzheimer's disease dementia, while dementia with Lewy bodies also constitutes a certain percentage<sup>2)</sup>.

For the FTDC criteria, although the  $\kappa$  values (indicating interrater agreement rate) are high, with 0.81 for possible bvFTD and 0.82 for probable bvFTD, there are some differences in agreement rate among individual items<sup>4)</sup>.

For characteristic image findings, see CQ8-2. Family history is evident in 30-50% of the patients in European and American countries but in almost none of the Japanese patients.

In the Diagnostic and Statistical Manual of Mental Disorders Fifth Edition (DSM-5), the term "neurocognitive disorder (NCD)" is introduced to replace the term "dementia. FTLD is called major or mild frontotemporal NCD, and broadly classified into behavioral variant and language variant. For diagnostic criteria of behavior variant, the criteria adopted are almost the same as the above-mentioned FTDC criteria.

#### 2. Diagnostic criteria of SD and characteristics of aphasia

According to the diagnostic criteria of Gorno-Tempini et al.<sup>5)</sup> the diagnostic procedure is first to diagnose progressive aphasia and then classify into semantic, non-fluent/grammatical, and logopenic (for classification based on aphasia, see CQ2-6). SD manifests semantic aphasia (loss of word meaning). However, in SD with predominantly right temporal lobe atrophy, some patients show conspicuous semantic deficits other than semantic aphasia (for example, semantic memory impairment related to well-known buildings and faces) or behavioral disorders in the early stage. Consequently, there is less consensus compared to the bvFTD diagnostic criteria. The diagnostic criteria for designated intractable diseases adopt the Gorno-Tempini diagnostic criteria for semantic variants characterized by aphasia, together with the diagnostic criteria of Neary et al.<sup>6)</sup> based on the evidence of characteristic semantic memory impairment regardless of the presence or absence of progressive aphasia.

In SD, impairment of object naming and word comprehension is consistent, and patients have difficulties with the same objects and words under different test settings and in daily life. Surface dyslexia is observed in reading kanjis that have different pronunciations, especially in idioms, where the words are read differently from the original kanjis.

Some patients develop impairment in recognizing the face of a known person, or cognitive impairments across multiple modalities such as visual and auditory comprehension of an object. These patients cannot recognize the faces of well-known persons, friends, or relatives whom they meet only occasionally. When they see these faces, they would say, "I can't remember anything" or "I don't know". The fact that recognition is not helped by providing sound or touch cues would indicate that

the condition is different from the usual agnosia.

For clinical diagnosis of SD, after identifying the characteristic aphasia, differentiate from other diseases such as Alzheimer's disease dementia carefully from image and other clinical findings.

### 3. Characteristics of aphasia observed in PNFA

Diagnostic criteria of nonfluent/agrammatic aphasia characteristic of PNFA have been reported by Gorno-Tempini et al.<sup>5)</sup>. As mentioned above, when using these criteria, first diagnose whether progressive aphasia is present. Nonfluent/agrammatic aphasia is characterized by (1) agrammatism in speech, and (2) apraxia of speech characterized by inconsistent speech sound errors and distortions (pronunciation not found in the Japanese language); at least one of the above should be present. While single-word comprehension is spared, comprehension of grammatically complex sentences is impaired. Other features are effortful speech, difficulty in initiating speech, halting speech, and inconsistent speech errors.

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#### ■ Search formula

PubMed search: July 10, 2015 (Friday)

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## What are the characteristics of image findings of frontotemporal lobar degeneration (FTLD)?

### Answer

Among FTLD disorders, behavioral variant frontotemporal dementia (bvFTD) shows MRI/CT findings of localized atrophy in the frontal and temporal lobes, predominantly in the frontal lobe. On SPECT/PET, decreased metabolism/decreased blood flow is observed in the frontal lobe and anterior temporal lobe, while the parietal and occipital lobes are spared.

Semantic dementia (SD) shows MRI/CT findings of atrophy in the temporal lobe predominantly involving the anterior region and inferior temporal gyrus. Usually, atrophy is asymmetrical. As the disease progresses, frontal lobe atrophy also appears. On SPECT/PET, decreased metabolism/decreased blood flow in the temporal lobe predominantly involving the anterior region and in the inferior temporal gyrus is observed.

Progressive non-fluent aphasia (PNFA) shows MRI/CT findings of atrophy in the left frontal lobe predominantly from the posterior region to the insula. On SPECT/PET, decreased metabolism/decreased blood flow in the left frontal lobe predominantly from the posterior region to the insula is observed.

Imaging examination is useful for the diagnosis of FTLD, but a diagnosis cannot be made with images alone. **B**

### Comments and evidence

#### 1. General head MRI/CT and SPECT/PET findings<sup>1)</sup>

For bvFTD, atrophy on MRI/CT and decreased metabolism and blood flow on SPECT/PET are observed in the frontal lobes and anterior temporal lobes. For SD, atrophy on MRI/CT and decreased metabolism/blood flow on SPECT/PET are observed in temporal lobes predominantly in the anterior region and in the inferior temporal gyrus. For PNFA, atrophy on MR/CT and decreased metabolism/blood flow are observed in the left frontal lobe predominantly from the posterior region to the insula.

#### 2. Brain volumetric imaging

Brain volumetric imaging is useful for the differentiation of Alzheimer's disease dementia, dementia with Lewy bodies, and FTLD<sup>2)</sup>.

In bvFTD, atrophy is observed in the frontal lobes involving the medial, dorsolateral, and orbitofrontal regions, as well as the anterior temporal lobes. Atrophy in the frontal lobe, especially the medial surface, progresses from the earliest stage<sup>1)</sup>. The results of a meta-analysis show that bvFTD is characterized by atrophy in the prefrontal cortex, in particular, atrophy of the regions corresponding to superior and middle frontal gyrus, anterior cingulate gyrus, insula, caudate nucleus, and putamen<sup>3)</sup>.

SD is characterized by left-right asymmetric inferior temporal gyrus-dominant anterior temporal atrophy or decreased blood flow/metabolism. The orbitofrontal cortex, insula, and caudate nucleus are also affected. In a longitudinal observational study, temporal lobe atrophy progresses from the earliest stage, and atrophy in the frontal lobe, insula, caudate nucleus, and thalamus progress in the same manner.

PNFA is characterized by atrophy or decreased blood flow/metabolism in the posterior frontal lobe, including Broca's area and the superior premotor cortex, as well as in the insula. Lesions in the superior temporal gyrus and striatum are also observed.

#### 3. Diffusion tensor imaging<sup>4)</sup>

In bvFTD, bilateral and widespread lesions in the white matter tracts are observed. The lesions are severe in the superior longitudinal fasciculus, anterior cingulate fasciculus, anterior corpus callosum, uncinate fasciculus, and inferior longitudinal fasciculus, and are especially severe, usually in the anterior aspect of superior longitudinal fasciculus and inferior longitudinal fasciculus. In SD, left-dominant degeneration in the uncinate fasciculus and inferior longitudinal fasciculus is observed, and anterior-dominant degeneration in the anterior corpus callosum and arcuate fasciculus is also found. In PNFA, degeneration is observed in the left superior longitudinal fasciculus, especially in the arcuate bundle projecting to the inferior frontal lobe.

#### 4. Resting-state functional MRI <sup>4)</sup>

In bvFTD, decreased connectivity of the salience network, including the anterior cingulate gyrus and the anterior insula has been reported.

#### 5. Genetic mutation and brain volumetric imaging <sup>5)</sup>

Compared to patients with mutations in *tau* and *progranulin* genes and patients with sporadic disease, patients with mutations in *C9orf72* gene show atrophy in the anterior temporal lobe, parietal lobe, occipital lobe, and cerebellum. Patients with *Tau* gene mutations are characterized by atrophy in the anteromedial temporal lobe, and patients with *progranulin* gene mutations are characterized by asymmetric atrophy in the temporoparietal lobe. In addition, the speed of atrophy of the brain as a whole is faster in patients with *progranulin* gene mutations than in patients with *C9orf72* or *tau* gene mutations.

#### 6. Comparison of brain imaging findings with underlying pathological findings <sup>6)</sup>

There is a limitation to estimate underlying pathology based on atrophy patterns observed on MRI. In recent years, highly sensitive tau PET imaging capable of visualizing tau pathology has become available in some facilities, and further studies are awaited <sup>7,8)</sup>.

#### 7. Phenocopy syndrome <sup>1)</sup>

Some bvFTD cases show no apparent atrophy on MRI, and they are termed “bvFTD phenocopy syndrome”. Clinical progression in these patients is known to be very slow. FDG-PET also does not show any abnormalities. Various underlying diseases, such as developmental disorders, are speculated.

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### ■ Search formula

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Ichushi search: July 10, 2015 (Friday)

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## Are there effective drugs for frontotemporal lobar degeneration (FTLD)?

### Recommendation

The use of selective serotonin reuptake inhibitor (SSRI) is recommended for the purpose of improving behavioral disorders in FTLD (off-label).

2C

### Comments and evidence

Because FTLD is a clinical syndrome and has diverse underlying pathologies, there are few studies on pharmacotherapy. The available studies are small-scale trials, which do not necessarily provide sufficient evidence<sup>1,2</sup>. A review reported by Nardell and Tampi<sup>2</sup> suggests that SSRIs, trazodone, and amphetamines may be effective in improving some behavioral symptoms, but none of the medications had an impact on cognition. The authors also pointed out various issues of the studies reviewed, such as the use of different diagnostic criteria, inconsistent evaluation indicators, and use of indicators such as Mini-Mental State Examination (MMSE) which are not sensitive to FTLD symptoms. Trazodone has been shown to be effective in a double-blind, randomized control trial (RCT)<sup>3</sup>.

Regarding SSRI, since the report of Swartz et al.<sup>4</sup> in 1997, some reports have shown that these drugs are effective for disinhibition, stereotyped behavior, and abnormal eating behavior, while other reports observed no effectiveness. In Japan, an open-label trial has reported the effectiveness of SSRI for repetitive behavior, stereotyped behavior, and compulsive complaint in FTLD<sup>5</sup>. Lanctot et al.<sup>6</sup> used PET to investigate the mechanism of action of SSRI for FTLD, and reported significant decreases in serotonin 5-HT<sub>1A</sub> receptor binding potential in all the brain regions examined in FTLD patients compared with controls. Using electroencephalography and magnetoencephalography, Hughes et al.<sup>7</sup> reported recovery of the activity of inferior frontal gyrus in FTLD patients treated with SSRI.

Views on the usefulness of cholinesterase inhibitors (ChEIs) remain divided<sup>1,2</sup>. There are reports of no effectiveness of ChEIs and reports of worsening of disinhibition. Thus caution is required when administering ChEIs. A recent review concludes that the efficacy of ChEIs for FTD cannot be confirmed and that ChEIs are associated with more gastrointestinal adverse effects<sup>8</sup>. Besides, two RCTs failed to demonstrate the usefulness of memantine, an NMDA receptor antagonist, compared with placebo.

Nasal oxytocin at a dose of 24 IU has been reported to improve the behavioral score of Neuropsychiatric Inventory (NPI) and reduce episodes of anger and fear compared with placebo<sup>9</sup>. Preparation of a large-scale and long-term clinical trial is ongoing<sup>10</sup>.

### References

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## ■ Search formula

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## Are there effective non-pharmacological therapies for frontotemporal lobar degeneration (FTLD)?

### Recommendation

Non-pharmacotherapy therapies such as care and behavioral therapy based on FTLD symptomatology are recommended.

2C

### Comments and evidence

The characteristics described in the diagnostic criteria for behavioral variant frontotemporal dementia (bvFTD) are essential in developing treatment strategies for behavioral disorders of FTLD.

Although there is little evidence, non-pharmacological therapies are useful and are the mainstay of treatment. In particular, by utilizing the patient's preserved functions and taking into account the characteristic symptoms and the patient's lifestyle, it may be possible to mitigate behavioral abnormalities and reduce the burden on caregivers<sup>1)</sup>.

Shinagawa et al.<sup>2)</sup> reviewed case reports, expert opinions, and clinical trials (excluding retrospective studies) of non-pharmacological management<sup>2)</sup>. Ikeda et al.<sup>3)</sup> studied six patients with FTLD, and reported that care that utilized the patient's preserved episodic memory, procedural memory, and visuospatial cognitive function was effective and resulted in the improvement of quality of life (QOL). Mioshi et al.<sup>4)</sup> and McKinnon et al.<sup>5)</sup> showed that a learning program comprising mainly of cognitive appraisal and coping strategies improved the burden on caregivers.

Ikeda et al.<sup>6)</sup> conducted a detailed assessment of behavioral disorders and behavioral interventions given to patients under hospitalized observation, and reported the effectiveness of conducting individualized family guidance based on behavioral disorder assessments of the patients and improvement of families' attitude toward the patients.

Lough et al.<sup>7)</sup> reported that the compulsive behaviors of a patient with FTLD were changed to socially acceptable behavior in response to behavioral modification techniques. Tokikawa et al.<sup>8)</sup> reported that the introduction of a daycare program for a patient with FTLD resolved the patient's obsessive-compulsive behaviors by acquiring a stereotyped behavior pattern. However, this report also pointed out the problems of newly acquired emotional compulsive behaviors such as coming to daycare, even on holidays, and not able to wait for the pick-up person.

Tokimasa et al.<sup>9)</sup> compared the cooking activities of 2 patients with FTLD and five patients with Alzheimer's disease dementia. In patients with Alzheimer's disease dementia, because of episodic memory impairment and apraxia, constant supervision is needed from the early stage, and acquisition of generalized compensation method is difficult. On the other hand, in patients with FTLD, after cautiously forming an intimate relationship, helping the patients form the habit of doing activities of daily living (ADL) utilizing stereotyped behavior is a crucial point for care.

In daycare and institutional care, reports have emphasized that to respond to severe mental symptoms; there is a need for one-on-one response at least when care is initiated<sup>6, 8, 10)</sup>. The usefulness of group homes where meticulous care can be provided has been reported<sup>11)</sup>.

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dementia" [TI] OR "frontotemporal lobe dementia" [TI] OR "frontal variant frontotemporal dementia" [TI]) AND Dementia/drug therapy
[Mesh]) OR ("frontotemporal lobar degeneration" OR "frontotemporal dementia" OR FTD OR FTLD OR bvFTD OR pick disease* OR picks
disease* OR "frontal lobe dementia" OR "frontotemporal lobe dementia" OR "frontal variant frontotemporal dementia") AND ("drug therapy" OR
chemotherapy OR pharmacotherapy OR "pharmacological therapy")) OR ("nonpharmacological therapy" OR "non pharmacological therapy" OR
"nonpharmacologic therapy" OR "non pharmacologic therapy" OR "nonpharmacological treatment" OR "non pharmacological treatment" OR
"nonpharmacologic treatment" OR "non pharmacologic treatment" OR nonpharmacological intervention* OR non pharmacological intervention*
OR nonpharmacologic intervention* OR non pharmacologic intervention* OR "nonpharmacological management" OR "non pharmacological
management" OR "nonpharmacologic management" OR "non pharmacologic management") AND ("Frontotemporal Lobar Degeneration" [Mesh]
OR "frontotemporal lobar degeneration" OR "frontotemporal dementia" OR FTD OR FTLD OR bvFTD OR pick disease* OR picks disease* OR
"frontal lobe dementia" OR "frontotemporal lobe dementia" OR "frontal variant frontotemporal dementia")OR "Frontotemporal Lobar
Degeneration/rehabilitation" [Mesh] OR("Frontotemporal Lobar Degeneration/therapy" [Mesh] AND "Rehabilitation" [Mesh]) OR
(("frontotemporal lobar degeneration" [TI] OR "frontotemporal dementia" [TI] OR FTD [TI] OR FTLD [TI] OR bvFTD [TI] OR pick disease*
[TI] OR picks disease* [TI] OR "frontal lobe dementia" [TI] OR "frontotemporal lobe dementia" [TI] OR "frontal variant frontotemporal
dementia" [TI]) AND (rehabilitation [TI] OR "occupational therapy" [TI] OR "activities of daily living" [TI] OR "activity of daily living" [TI]))
OR ("frontotemporal lobar degeneration" OR "frontotemporal dementia" OR FTD OR FTLD OR bvFTD OR pick disease* OR picks disease*
OR "frontal lobe dementia" OR "frontotemporal lobe dementia" OR "frontal variant frontotemporal dementia") AND (rehabilitation OR
"occupational therapy" OR "activities of daily living" OR "activity of daily living")) OR "Frontotemporal Lobar Degeneration/nursing" [Mesh] OR
("Frontotemporal Lobar Degeneration/ therapy" [Mesh] AND "Nursing" [Mesh]) OR ("frontotemporal lobar degeneration" [TI] OR
"frontotemporal dementia" [TI] OR FTD [TI] OR FTLD [TI] OR bvFTD [TI] OR pick disease* [TI] OR picks disease* [TI] OR "frontal lobe
dementia" [TI] OR "frontotemporal lobe dementia" [TI] OR "frontal variant frontotemporal dementia" [TI])AND nursing [TI] OR(("frontotemporal
lobar degeneration" OR "frontotemporal dementia" OR FTD OR FTLD OR bvFTD OR pick disease* OR picks disease* OR "frontal lobe
dementia" OR "frontotemporal lobe dementia" OR "frontal variant frontotemporal dementia")AND nursing)OR "Frontotemporal Lobar
Degeneration/diet therapy" [Mesh] OR ("Frontotemporal Lobar Degeneration/therapy" [Mesh] AND "Nutrition therapy" [Mesh]) OR
(("frontotemporal lobar degeneration" [TI] OR "frontotemporal dementia" [TI] OR FTD [TI] OR FTLD [TI] OR bvFTD [TI] OR pick disease*
[TI] OR picks disease* [TI] OR "frontal lobe dementia" [TI] OR "frontotemporal lobe dementia" [TI] OR "frontal variant frontotemporal
dementia" [TI]) AND (nutrition therapy* [TI] OR diet therapy* [TI])) OR ("frontotemporal lobar degeneration" OR "frontotemporal dementia"
OR FTD OR FTLD OR bvFTD OR pick disease* OR picks disease* OR "frontal lobe dementia" OR "frontotemporal lobe dementia" OR "frontal
variant frontotemporal dementia") AND (nutrition therapy* OR diet therapy*))OR "Frontotemporal Lobar Degeneration/ surgery" [Mesh]
OR("Frontotemporal Lobar Degeneration/therapy" [Mesh]AND "Surgical Procedures, Operative" [Mesh]) OR ("frontotemporal lobar
degeneration" [TI] OR "frontotemporal dementia" [TI] OR FTD [TI] OR FTLD [TI] OR bvFTD [TI] OR pick disease* [TI] OR picks disease*
[TI] OR "frontal lobe dementia" [TI] OR "frontotemporal lobe dementia" [TI] OR "frontal variant frontotemporal dementia" [TI]) AND (surgery
[TI] OR surgical [TI] OR operation [TI] OR operative [TI])) OR ("frontotemporal lobar degeneration" OR "frontotemporal dementia" OR FTD
OR FTLD OR bvFTD OR pick disease* OR picks disease* OR "frontal lobe dementia" OR "frontotemporal lobe dementia" OR "frontal variant
frontotemporal dementia") AND (surgery OR surgical OR operation OR operative)) OR "Frontotemporal Lobar Degeneration/radiotherapy"
[Mesh] OR ("Frontotemporal Lobar Degeneration/therapy" [Mesh] AND "Radiotherapy" [Mesh]) OR ("frontotemporal lobar degeneration" [TI]
OR "frontotemporal dementia" [TI] OR FTD [TI] OR FTLD [TI] OR bvFTD [TI] OR pick disease* [TI] OR picks disease* [TI] OR "frontal
lobe dementia" [TI] OR "frontotemporal lobe dementia" [TI] OR "frontal variant frontotemporal dementia" [TI]) AND (radiotherapy* [TI] OR
chemoradiotherapy* [TI] OR radiosurgery* [TI])) OR ("frontotemporal lobar degeneration" OR "frontotemporal dementia" OR FTD OR FTLD
OR bvFTD OR pick disease* OR picks disease* OR "frontal lobe dementia" OR "frontotemporal lobe dementia" OR "frontal variant frontotemporal
dementia") AND (radiotherapy* OR chemoradiotherapy* OR radiosurgery*)) OR ("Frontotemporal Lobar Degeneration/therapy" [Mesh]AND
"Psychotherapy" [Mesh]) OR ("frontotemporal lobar degeneration" [TI] OR "frontotemporal dementia" [TI] OR FTD [TI] OR FTLD [TI] OR
bvFTD [TI] OR pick disease* [TI] OR picks disease* [TI] OR "frontal lobe dementia" [TI] OR "frontotemporal lobe dementia" [TI] OR "frontal
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variant frontotemporal dementia" [TI]) AND psychotherapy\* [TI]) OR (("frontotemporal lobar degeneration" OR "frontotemporal dementia" OR FTD OR FTLD OR bvFTD OR pick disease\* OR picks disease\* OR "frontal lobe dementia" OR "frontotemporal lobe dementia" OR "frontal variant frontotemporal dementia")AND psychotherapy\*) OR ("Frontotemporal Lobar Degeneration/therapy" [Mesh]AND "Patient Care" [Mesh]) OR (("frontotemporal lobar degeneration" [TI] OR "frontotemporal dementia" [TI] OR FTD [TI] OR FTLD [TI] OR bvFTD [TI] OR pick disease\* [TI] OR picks disease\* [TI] OR "frontal lobe dementia" [TI] OR "frontotemporal lobe dementia" [TI] OR "frontal variant frontotemporal dementia" [TI]) AND (care [TI] OR cares [TI])) OR (("frontotemporal lobar degeneration" OR "frontotemporal dementia" OR FTD OR FTLD OR bvFTD OR pick disease\* OR picks disease\* OR "frontal lobe dementia" OR "frontotemporal lobe dementia" OR "frontal variant frontotemporal dementia") AND (care OR cares))

Ichushi search: July 9, 2015 (Thursday)

#1 (((Frontotemporal lobar degeneration/TH OR Frontotemporal lobar degeneration/TI OR Dementia-frontotemporal type/TH OR Frontotemporal type dementia/TI OR "Frontotemporal Lobar Degeneration"/TI OR "Frontotemporal Dementia"/TI OR FTD/TI OR FTLD/TI OR bvFTD OR Pick disease/TI OR Pick disease OR Anterior type dementia/TI OR Anterior type dementia/TI OR Frontotemporal dementia/TI) AND ((SH = Therapeutic use, Treatment, Surgical therapy, Transplantation, Dietary therapy, Radiotherapy, Nursing, Rehabilitation, Prevention)OR Treatment/MTH OR Treatment/TI OR Therapy/TI)) NOT ((Frontotemporal lobar degeneration/TH OR Frontotemporal lobar degeneration/TI OR Dementia-frontotemporal type/TH OR Frontotemporal type dementia/TI OR "Frontotemporal Lobar Degeneration"/TI OR "Frontotemporal Dementia"/TI OR FTD/TI OR FTLD/TI OR bvFTD OR Pick disease/TI OR Pick disease OR Anterior type dementia/TI OR Anterior type dementia/TI OR Frontotemporal dementia/TI) AND ((SH = Pharmacotherapy) OR Pharmacotherapy/TH OR Therapeutic use/MTH OR Drug treatment/TI OR Pharmacotherapy/TI OR Therapeutic drug/TI))) OR ((Frontotemporal lobar degeneration/TH OR Frontotemporal lobar degeneration/TI OR Dementia-frontotemporal type/TH OR Frontotemporal type dementia/TI OR "Frontotemporal Lobar Degeneration"/TI OR "Frontotemporal Dementia"/TI OR FTD/TI OR FTLD/TI OR bvFTD OR Pick disease/TI OR Pick disease OR Anterior type dementia/TI OR Anterior type dementia/TI OR Frontotemporal dementia/TI) AND ((SH = Surgical therapy, Transplantation, Radiation therapy, Dietary therapy, Psychological therapy, Nursing, Rehabilitation) OR Non-pharmacotherapy/TI OR Non-pharmacological treatment/TI OR Rehabilitation/MTH OR Rehabilitation/TI OR Nursing/MTH OR Nursing/TI OR Surgical operation/MTH OR Surgery/TI OR Surgery/TI OR Transplantation/TI OR Nutritional management/MTH OR Nutritional therapy/TI OR Dietary therapy/TI OR Diet therapy/TI OR Therapeutic food/TI OR Psychological therapy/TH OR Psychological therapy/TI OR Psychotherapy/TI OR Psychotherapy/TI OR Radiation treatment/MTH OR Radiation treatment/TI OR Radiation therapy/TI))

## What kind of instructions should be given to families and caregivers of frontotemporal lobar degeneration (FTLD) patients?

### Answer

Family and caregiver education based on FTLD symptomatology is recommended.



### Comments and evidence

In FTLD, psychiatric symptoms and behavioral disorders such as disinhibition, asocial behaviors, stereotypic behaviors, abnormal eating behaviors, and increased emotional susceptibility become evident from an earlier stage compared to Alzheimer's disease dementia<sup>1-3</sup>. Due to these various behavioral disorders, caregivers of FTLD patients have a more significant care burden than caregivers of Alzheimer's disease dementia patients<sup>4-7</sup>. Based on the assessments of patients' behavioral abnormalities and language impairment, it is vital to help patients' families understand the disease conditions of individual patients and to provide them guidance on interventions. Also, FTLD has been designated an intractable disease in Japan since July 1, 2015, and it is imperative to explain and provide guidance on how to apply for a subsidy of medical expenses.

Kumamoto et al.<sup>7</sup> studied two FTLD patients and found that behavioral abnormalities exhibited by these patients, particularly behaviors of stuffing food into the mouth, poor table manners, resistance to care, and restlessness, were associated with substantial care burden<sup>7</sup>. Therefore, for family caregivers, individual guidance and support are required according to the patient's conditions. Understanding of the disease condition by the family changes the way caregivers interact with the patients, and the burden on caregivers is often significantly reduced<sup>8</sup>.

Nunnemann et al.<sup>9</sup> pointed out that there are very few publications on the burden, problems, and needs of caregivers of FTLD patients. Specific problems include delayed diagnosis, young-onset age, behavioral disturbances, lack of information and suitable care facilities, caregivers' depression, social isolation, and personal needs. Research is needed to identify the real needs of caregivers of FTLD patients.

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### Search formula

PubMed search: July 10, 2015 (Friday)

#1 ("Frontotemporal Lobar Degeneration" [Majr] OR "frontotemporal lobar degeneration" [TI] OR "frontotemporal dementia" [TI] OR FTD [TI] OR FTLD [TI] OR bvFTD [TI] OR Pick disease\* [TI] OR Picks disease\* [TI] OR "frontal lobe dementia" [TI] OR "frontotemporal lobe dementia" [TI] OR "frontal variant frontotemporal dementia" [TI]) AND (care OR education OR burden OR support\*) AND (caregiver\* OR family)

Ichushi search: July 10, 2015 (Friday)

#1 (Frontotemporal lobar degeneration/TH OR Frontotemporal lobar degeneration/TI OR Dementia-frontotemporal type/TH OR Frontotemporal type dementia/TI OR "Frontotemporal Lobar Degeneration"/TI OR "Frontotemporal Dementia"/TI OR FTD/TI OR FTLD/TI OR bvFTD OR Pick disease/TI OR Pick disease OR Anterior type dementia/TI OR Anterior type dementia/TI OR Frontotemporal dementia/TI) AND (Family/TH OR Family OR Caregiver/TH OR Care) AND (Care burden/TH OR Burden OR Stress/TH OR Stress OR Guidance OR Education OR Support)