Variations in regional SPECT hypoperfusion and clinical features in frontotemporal dementia

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Abstract—*Objective:* To characterize the presenting clinical features for frontotemporal dementia (FTD) and contrast them with the degree of frontal and temporal hypoperfusion on SPECT imaging. *Methods:* The authors evaluated 74 patients who eventually met Consensus Criteria for the FTD form of frontotemporal lobar degeneration (excluding primary progressive aphasia and semantic dementia) on 2-year follow-up. On first presentation, these patients had undergone both an FTD Inventory for 12 features based on core and supportive Consensus Criteria and SPECT imaging. The initial clinical diagnostic features were contrasted with variations in regional SPECT hypoperfusion. *Results:* The patients with FTD had more hypoperfusion in the right frontal lobe than in other regions; the subgroup of 25 patients who met Consensus Criteria from the first presentation had the most right frontal hypoperfusion. Frontal lobe involvement was associated with significant apathy, whereas temporal lobe involvement was associated with hypomania-like behavior. Right frontal lobe hypoperfusion further predicted loss of insight, environmental dependency, and stereotyped behaviors. Other associations included left frontal hypoperfusion with a decline in personal hygiene and left temporal hypoperfusion with compulsions and mental rigidity. *Conclusions:* On first presentation, frontotemporal dementia (FTD) is disproportionately a right frontal disease evident on behavioral measures and on SPECT. Nonetheless, patients with FTD can initially present with further regional differences in clinical diagnostic features, such as apathy with bifrontal hypoperfusion and hypomania-like behaviors with anterior temporal involvement.

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Frontotemporal dementia (FTD) is a clinicopathologic syndrome with prominent behavioral symptoms and progressive degeneration of the frontal lobes, anterior temporal lobes, or both.[1-4] The most common clinical criteria for diagnosing FTD, the Consensus Criteria,[5] miss most patients with FTD at onset of their disease.[6-8] A major reason for this failure is the variability in early regional involvement of the disease.[1-3] There can be significant hemispheric asymmetry associated with the earliest presentation of FTD, resulting in different behavioral manifestations.[9,10] Moreover, FTD is associated with different extent of pathology in frontal and anterior temporal regions.[6] The degree of frontal vs temporal pathology can account for further variability in the presenting clinical symptoms of FTD.[11] Although others have looked at localization of behavior in FTD, no study has specifically evaluated the extent of early variations in regional involvement on the diagnostic criteria for this disorder.

In this study, we compared variations in functional neuroimaging and the nature of presenting behavioral features in a large series of patients with FTD who eventually met Consensus Criteria for FTD.[5] The patients underwent SPECT on first presentation. These images were independently coded on the degree of frontal or temporal hypoperfusion. The SPECT results were then compared to an FTD inventory of 12 presenting behavioral symptoms reflecting both core and supportive diagnostic features of the Consensus Criteria for FTD.[5]

Methods. *Subjects.* All participants in this study presented for evaluation to university-affiliated specialty clinics in dementing disorders. The patients were community-based, moderately impaired patients who underwent a comprehensive neurobehavioral evaluation, laboratory assessment, and MRI of the brain. The patients were screened for chronic mental illness, head trauma, vascular dementia, extrapyramidal disorders, vitamin deficiency, hypothyroidism, syphilis, and other medical conditions. Finally, every subject underwent technetium Tc 99m hexamethyl propylenamine oxime SPECT imaging as part of their initial diagnostic assessment.

All patients with FTD included in this study presented with the insidious onset and progression of cognitive and behavioral changes and were followed up for at least a 2-year period. Consensus Criteria for FTD were applied on first presentation and again on 2-year follow-up. The necessary core features of Consensus Criteria do not include neuroimaging such as SPECT. They in-

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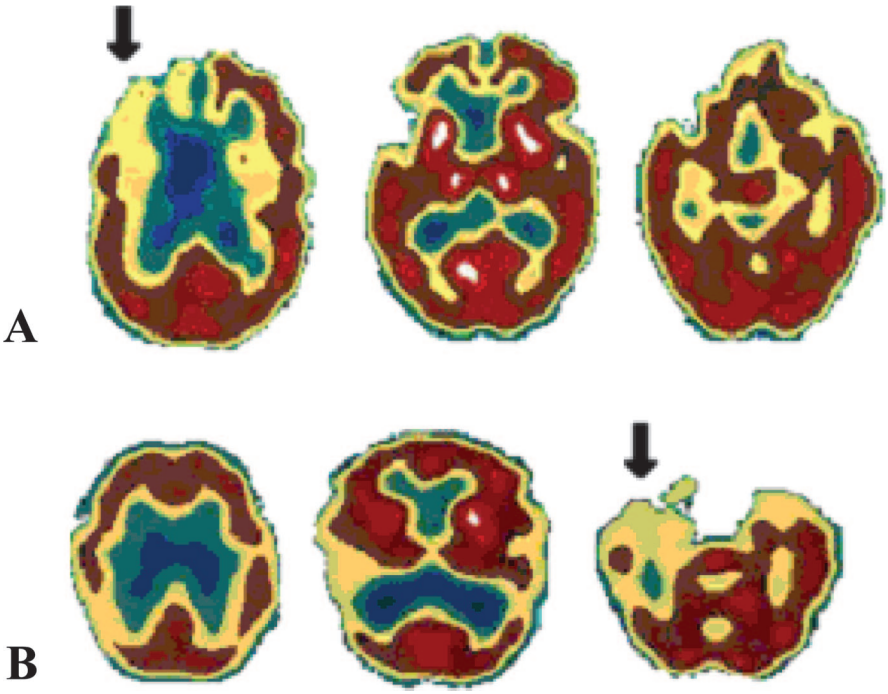

Figure 1. (A) Example of SPECT scan rating on a patient with predominant right frontal hypoperfusion. Lobar ratings were 3 for right frontal, 1 for left frontal, 2 for right temporal, and 1 for left temporal. (Radiology convention: left is on the right side and right is on the left side.) (B) Example of SPECT scan rating on a patient with predominant right temporal hypoperfusion. Lobar ratings were 1 for right frontal, 1 for left frontal, 3 for right temporal, and 1 for left temporal. (Radiology convention: left is on the right side and right is on the left side.)

clude evidence of declines in social interpersonal conduct, regulation of personal conduct, emotional expression, and insight.[5] Only patients who met these Consensus Criteria for FTD at the 2-year follow-up were included in this study. Patients with other frontotemporal lobar degenerations, such as primary progressive aphasia and semantic dementia, were not included.[5] Study participation included written informed consent according to institutional review board guidelines.

Procedures. The initial clinical SPECT scans were re-read by two independent and experienced raters, blind to the clinical diagnosis. This technique has been previously reported.[13] The blinded visual re-inspections of the clinical SPECT scans used a quadrant approach. Specifically, the rater graded the scans for hypoperfusion on a 0- to 4-point scale (0 = absent, 1 = mild, 2 = moderate, 3 = severe) for each of left frontal, right frontal, left anterior temporal, and right anterior temporal regions (figure 1). For the two raters, the inter-rater reliability for this re-inspection was high ($r_s = 0.714$ for 296 ratings, $p < 0.001$).

Neurologists evaluated the patients with an FTD Inventory on first presentation (table 1). The neurologists completed the FTD Inventory after a structured interview with the patient and the informant or caregiver. Most of the information came from the informant's report of changes in the patient's behavior from his or her lifelong premorbid state. The behaviors included in the inventory were derived from specifications of the Consensus Criteria, core and supportive diagnostic features.[5] The investigators coded the items on the FTD Inventory on a five-point Likert scale from "Not at All Characteristic" to "Extremely Characteristic." The inter-rater reliability on the FTD Inventory for two participating neurologists was calculated for seven patients (weighted k range for the 12 items = 0.42 to 0.67, "moderate to good" agreement).

FTD Inventory items based on Consensus Criteria—core diagnostic features. The core feature of an insidious onset and gradual progression was part of the initial presentation and not included on the FTD Inventory.[5] The remaining four core features included behavioral measures that required further operationalization: 1. An early decline in "social interpersonal conduct" referred to qualitative breeches of etiquette incongruent with the patient's premorbid behavior. As defined, this included both behavioral disinhibition and violations of social norms not necessarily consequent to disinhibition. Accordingly, this feature was split into two items on the FTD Inventory (see table 1). 2. Early impairment in regulation of personal conduct referred to quantitative changes in behavior ranging from passivity and inertia to overactivity and hypomania-like behaviors. Accordingly, this feature was split into two items on the FTD Inventory. 3. Early emotional blunting was specified as a loss of emotional warmth and empathy. 4. Loss of insight was specified as decreased awareness of behavioral changes.

FTD Inventory items based on Consensus Criteria—supportive diagnostic features. The six supportive features[5] were identical to the non-speech-language behavioral criteria with slight modification: 1. Perseverative and stereotyped behavior included com-

Table 1 *Frontotemporal Dementia Inventory*

Items based on Consensus Criteria—core diagnostic features
1. Behavioral disinhibition (verbal, physical, or sexual)
2. Violation of social norms (loss of social tact or propriety or antisocial acts)
3. Apathy (passivity, inertia, and inactivity)
4. Hypomania-like behavior (overactivity, excessive talking, laughing, singing, sexuality)
5. Loss of interpersonal warmth or empathy
6. Loss of insight (for their behavioral changes)
Items based on Consensus Criteria—supportive diagnostic features
7. Decline in personal hygiene and grooming
8. Mental rigidity and inflexibility
9. Distractibility and impersistence
10. Hyperorality and dietary changes (including food fads)
11. Compulsive or stereotyped behavior
12. Environmental dependency (utilization, stimulus-bound, or imitation behavior)

After completion of the initial evaluation, the investigator decides the degree to which each of the listed items is a characteristic change in the patient's current state or behavior, then places a number between "1" and "5" in the correct space according to the following scale: 1 = not at all characteristic; 2 = slightly characteristic; 3 = moderately characteristic; 4 = very characteristic; 5 = extremely characteristic.

pulsions; therefore, the category was renamed "compulsions and stereotyped behavior." The individual responses were further reviewed for whether they were more like complex compulsions or simple stereotyped behaviors. 2. Utilization behavior was expanded to include environmental dependency behavior in general, such as stimulus-bound and imitation behaviors.

Data analysis. Demographic characteristics were compared using two-tailed t tests and χ^2 analysis as appropriate. A repeated measures analysis evaluated the four quadrant ratings of the SPECT findings, and two-tailed t tests evaluated the impact of SPECT findings on initial diagnosis. Multivariate analysis of variance (MANOVA) compared neuroimaging scores with the behavioral variables. There were two MANOVAs: one for the items based on core diagnostic features and another for items based on supportive diagnostic features. Given the two MANOVAs, a conservative p level of <0.025 was set for the post hoc significance of specific behaviors. Ordinal regression further evaluated the degree of association between the SPECT ratings and the FTD Inventory items. Given the 12 regression analyses, a conservative Bonferroni p level of <0.005 was set for the significance of the SPECT–feature associations.

Results. This study identified 74 FTD subjects who met Consensus Criteria (all five of the core features) at 2-year follow-up, only 25 (33.8%) of whom had met Consensus Criteria on first presentation. There were 36 men and 38 women with 15.1 (3.2) years of education and Mini-Mental State Examination (MMSE) scores of 22.6 (5.3).[12] The age at onset was 57.7 (10.5) years, and the age at presentation was 60.9 (10.9) years. There were no differences between the males and females on the SPECT rating scores or any of the 12 behavioral variables. There were no correlations between years of education, MMSE scores, age at onset, or age at presentation and either SPECT rating scores or any of the 12 items of the FTD Inventory.

SPECT findings. The total SPECT hypoperfusion ratings for the two raters included means of 1.88 (0.95) for left frontal, 2.14 (0.90) for right frontal, 1.36 (0.79) for left temporal, and 1.73 (1.00) for right temporal regions. Repeated measures analysis showed overall differences in regions of hypometabolism ($F = 9.92$, $p < 0.001$). Post hoc analysis showed that there was greater overall hypoperfusion in the right frontal region compared to each of the other three quadrants (vs left temporal: $F = 24.08$, $p < 0.001$; vs left frontal: $F = 7.72$, $p = 0.007$; vs right temporal: $F = 6.54$, $p = 0.013$). Among patients with FTD who were rated with either moderate or severe (2 or 3) hypoperfusion on the SPECT scans, there were 59 with right frontal hypoperfusion, 50 with left frontal hypoperfusion, 44 with right temporal hypoperfusion, and 35 with left temporal hypoperfusion (Cochran's $Q = 17.65$, df 3, $p < 0.001$). The 25 patients who met Consensus Criteria on first presentation had more right frontal hypoperfusion on SPECT than the remaining 49 patients who did not meet initial Consensus Criteria ($t = 2.58$; $p = 0.01$) (figure 2).

Core diagnostic features. For the FTD Inventory items based on core diagnostic features (table 2), there was an overall difference depending on areas of hypoperfusion ($F = 611.09$, $p < 0.001$). The following were significant: left frontal hypoperfusion with apathy ($F = 29.89$, $p < 0.001$); right frontal hypoperfusion with both apathy ($F = 32.72$, $p < 0.001$) and loss of insight ($F = 14.45$, $p < 0.001$); left temporal hypoperfusion with hypomania-like behavior ($F = 6.54$, $p = 0.001$); right temporal hypoperfusion with hypomania-like behavior ($F = 3.68$, $p = 0.013$). These results were substantiated by the significant associations (likelihood ratio tests) of regional SPECT hypoperfusion with apathy ($\chi^2 = 138.26$, df 12, $p < 0.001$; primarily with right frontal and left frontal hypoperfusion), hypomanic-like behavior ($\chi^2 = 112.43$, df 12, $p < 0.001$; primarily with right temporal and left temporal hypoperfusion), and loss of insight ($\chi^2 = 55.68$, df 12, $p < 0.001$; primarily from right frontal hypoperfusion).

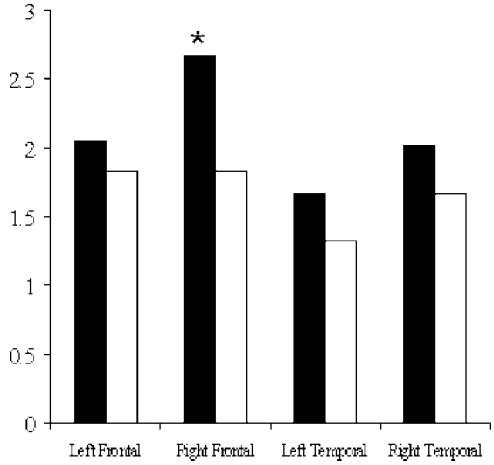

*Figure 2. Regional SPECT hypoperfusion among the 74 patients with frontotemporal dementia (FTD). Differences between patients with FTD depending on whether they met Consensus Criteria on first presentation. Shaded column = patients (n = 25) who met Consensus Criteria on first presentation and at 2-year follow-up. Unshaded column = patients (n = 49) who did not meet Consensus Criteria on first presentation but did meet Consensus Criteria at 2-year follow-up. *Significant difference, t = 2.58, p = 0.01. Values on Y-axis represent mean hypoperfusion scores, rated by visual inspection for the quadrant according to a 0- to 4-point scale (0 = absent, 1 = mild, 2 = moderate, 3 = severe).*

Supportive diagnostic features. For the FTD Inventory items based on supportive diagnostic features, there was also a difference depending on areas of hypoperfusion ($F = 397.50$, $p < 0.001$). The following were significant: left

Table 2 *Means and standard deviations for Frontotemporal Dementia Inventory scores*

Items	Mean	SD
Based on core diagnostic features		
Behavioral disinhibition	3.07	1.00
Violation of social norms	3.32	1.07
Apathy	3.36	1.50
Hypomanic-like behavior	3.00	1.25
Loss of interpersonal warmth or empathy	2.66	0.94
Loss of insight	3.19	1.21
Based on supportive diagnostic features		
Decline in personal hygiene and grooming	2.86	0.90
Mental rigidity and inflexibility	2.62	0.90
Distractibility and impersistence	3.38	0.87
Hyperorality and dietary changes	3.08	1.24
Compulsive or stereotyped behavior	3.26	1.21
Environmental dependency	2.47	1.37

frontal hypoperfusion with decreased personal hygiene ($F = 4.77$, $p = 0.006$); right frontal hypoperfusion with both compulsive or stereotyped behavior ($F = 5.27$, $p = 0.01$) and environmental dependency ($F = 17.01$, $p < 0.001$); left temporal hypoperfusion with both mental rigidity ($F = 5.31$, $p = 0.004$) and compulsive or stereotyped behavior ($F = 3.59$, $p = 0.02$). Retrospective analysis of the individual compulsive or stereotyped behaviors suggested that patients with FTD and high left temporal hypoperfusion had more compulsive acts and patients with FTD and high right frontal hypoperfusion had more simple stereotyped behaviors. These results were substantiated by the associations (likelihood ratio tests) of regional SPECT hypoperfusion with mental rigidity and inflexibility ($\chi^2 = 34.91$, df 12, $p < 0.001$), compulsive or stereotyped behavior ($\chi^2 = 33.99$, df 12, $p < 0.001$; primarily from right frontal hypoperfusion), and environmental dependency ($\chi^2 = 64.46$, df 12, $p < 0.001$; primarily from right frontal hypoperfusion).

Discussion. Variations in regional involvement significantly influence the nature of the presenting symptoms of FTD. Patients with right frontal disease are more likely to meet initial Consensus Criteria for FTD and have apathy, loss of insight, and other behaviors consistent with the diagnostic features for this disorder.[7] In this study, early frontal hypoperfusion of both hemispheres was associated with apathy, and early temporal perfusion of both hemispheres was associated with hypomania-like behaviors. Among these patients with FTD, there were other behavioral differences associated with variations in regional hypoperfusion.

The early diagnosis of FTD can be difficult to make on initial presentation. In the absence of a definitive clinical test, this diagnosis relies on behavioral criteria. Suspicion of FTD arises when there are behavioral changes often associated with frontotemporal abnormalities on neuroimaging.[5,14,15] Experts developed the Consensus Criteria for the diagnosis of FTD.[5] Despite selected reports of high sensitivities and specificities for diagnosing this disorder,[16] clinicians frequently misdiagnose FTD.[17-19] A reason for the inadequacy of the clinical criteria for FTD is the large degree of anatomic variability early in this disease.

A major early anatomic variable in FTD is the degree of hemispheric asymmetry. Patients with left hemisphere FTD have early speech and language difficulty but more normal behavior compared to patients with right hemisphere FTD.[9,10,20] In contrast, patients with right hemisphere FTD have preserved speech and language but often manifest socially undesirable behavior and a flattened and non-empathic affect with decreased facial expressions.[9-11,13,21] In comparison to the left hemisphere patients, patients with right hemisphere FTD have worse performance IQs, design fluency, and picture arrangement, and they have more perseverations and conceptual errors on the Wisconsin Card Sort Test.[9,10,20,22-24] This study confirmed the presence of predominant right hemispheric involvement in FTD but also indicated that other anatomic variables affect the early clinical features of this disease.

Another major anatomic variable in FTD is the degree of frontal vs temporal involvement. Patients with frontal FTD manifest apathy, decreased social dominance, and a dysexecutive personality change.[25-27] Those with right greater than left frontal involvement show behavioral disinhibition, altered nonverbal behavior, and diminished maintenance of previously learned self-concepts.[9,13,28,29] Patients with temporal FTD, which usually involves the adjacent orbitofrontal lobe, manifest interpersonal coldness and impairments in emotional processing.[8,27] Those with right greater than left temporal involvement show major personality changes including emotional disturbances, bizarre alterations in dress, limited and fixed ideas, and increased visual alertness.[10,11,13] Additional investigations have compared FTD with predominantly frontal involvement and semantic dementia, a frontotemporal lobar degeneration with semantic deficits from temporal involvement. They report that patients with FTD (with frontal involvement) have disinhibition, social avoidance, reduced response to pain, gluttony, and indiscriminate eating.[30,31]

In this study, patients with frontal FTD tended to hypoactivity and apathy, whereas patients with temporal FTD tended to hypomania-like behavior. Compared to AD, apathy and negative symptoms are more prominent among patients with FTD and occur at earlier stages of their disease.[32,33] MRI volumetric measurements on patients with FTD have shown that this apathy correlates with frontal lobe atrophy.[25] Some reports suggest that apathy occurs with symptoms that are particularly referenced to the right frontal lobe.[32,34] In contrast, many of the FTD Consensus Criteria symptoms described as quantitative disturbances of "personal regulation" are hypomania-like.[5] Euphoria and increased mood or jocularity and "Witzelsücht" occur in about one-third of patients with FTD and often correspond to right anterior temporal plus adjacent orbitofrontal disease.[11,35] When accompanied with disinhibition or restlessness, these patients with FTD can resemble those with primary mania or hypomania.

Repetitive behaviors are also common in FTD.[31,36-38] Patients with right frontal FTD can have simple repetitive acts and verbal or motor stereotypies such as hand rubbing or clapping, swaying, grimacing, and lip pursing or smacking.[38] These behaviors may result from an inability to inhibit existing programs or urges or to override environmentally dependent stimulus-driven behavior.[36,39] On the other hand, patients with temporal FTD can have complex or compulsive-like repetitive behaviors.[31,37] Compulsions are common presenting symptoms among patients with FTD and encompass repetitive motor routines such as repetitive checking, cleaning, vocalizations, collecting and hoarding objects, counting money, and rituals involving unusual toileting behavior.[39,40] The results reported here suggest that

left temporal disease is more critical than right for compulsions in FTD.

Three other presenting behaviors were localized in this study. First, decreased insight, a common symptom of FTD, was associated with right frontal hypoperfusion. Other studies in both Alzheimer disease and FTD have shown an association of decreased insight with right frontal deficits or hypoperfusion on SPECT.[13,29,41-43] The loss of insight in FTD may result from a loss of concern for their illness, mediated by a loss of self-referential behavior in the right frontal lobe.[13,28] Second, right frontal hypoperfusion was associated with environmentally dependent behavior such as utilization or stimulus-bound behaviors. This may be consistent with reports of a greater tendency to perseverations in patients with right frontal FTD.[10,20,22] Third, there was an association between decreased hygiene and grooming and left frontal hypoperfusion. The reason for this relationship is less unclear, although it could have resulted from executive disturbances or decreased mood in the presence of relatively preserved insight.

This clinical study has strengths and potential weaknesses. Strengths include the inclusion of a large number of well-studied patients with FTD, 2-year follow-ups with Consensus Criteria, and the availability of SPECT scans for re-visualization. Conversely, this study did not include patients with other frontotemporal lobar degenerations, such as primary progressive aphasia or semantic dementia; this could have slanted the findings toward greater right frontal hypoperfusion. The findings, however, speak to the fact that the clinical diagnostic criteria for FTD strongly select for right hemisphere dysfunction. Moreover, the findings indicate that other anatomic variables, such as frontal vs temporal involvement, affect the initial clinical presentation of FTD. Finally, an additional limitation of this study was the use of visual coding of SPECT scans rather than precisely quantitative measurements; small areas of hypoperfusion could have been missed or underestimated. The focus, however, was on demonstrating larger hemispheric or lobar associations between regional hypoperfusion and clinical diagnostic features in FTD.

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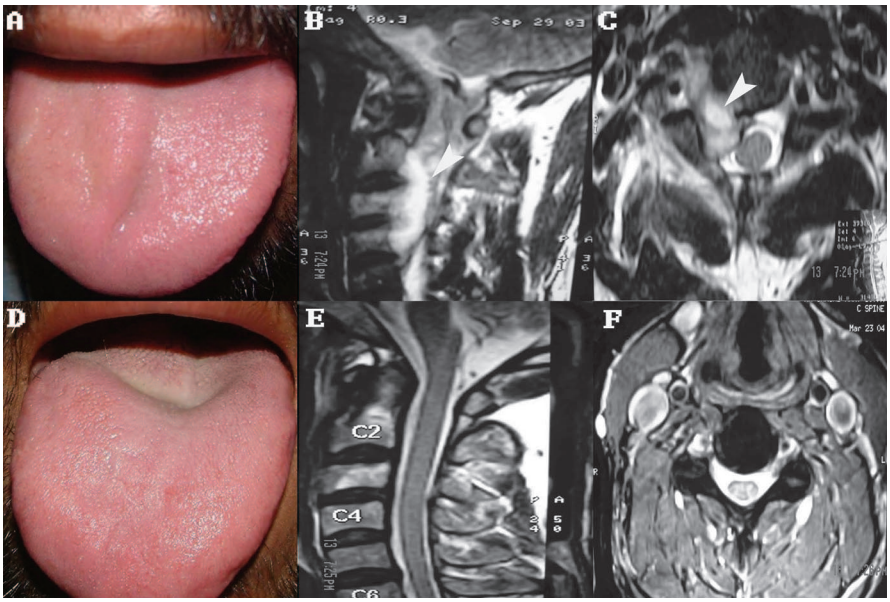

Figure.(A) Deviation of tongue to right side with atrophy on the right side. (B and C) Sagittal and axial sections of MRI, T2-weighted image showing large epidural abscess extending from C1 to C4 predominantly on the right side (arrow, B) and extending to neural foramina (arrow, C). There is evidence of destruction of C3 vertebral body with normal intervertebral disc space. (D, E, F) After 1.5 years of antitubercular treatment. (D) Improvement in tongue deviation and muscle bulk on the right side. (E and F) Sagittal and axial section of MRI, T2-weighted image showing regression of epidural abscess with residual hyperintense signal of C2 and C3 vertebral bodies.

Hypoglossal nerve paralysis caused by high cervical epidural abscess

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A 32-year-man noticed deviation of his tongue to the right side for 2 weeks. He had no history of fever, weight loss, or neck pain. Examination revealed deviation of the tongue to the right with atrophy (figure, A). MRI showed an epidural abscess extending from C1 to C4, predominantly on the right side (figure, B and C). The patient was given antitubercular treatment for 1.5 years. He received corticosteroid treatment for the initial 6 weeks. The tongue deviation and bulk improved (figure, D) with regression of epidural abscess (figure, E and F). It is possible that the hypoglossal nerve was compressed at nasopharyngeal/oropharyngeal carotid space.[1]

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