Differential diagnosis of Frontotemporal Dementia FTLD using visual rating scales

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Aims and objectives

Frontotemporal lobar degeneration (FTLD) represents the second most common early onset of neurodegenerative dementia in those less than 65 years of age [1]. The overlap between different kinds of Frontotemporal dementia is variable, constituting a source of uncertainty that clinicians would wish to rule out. FTLD is associated with several clinical syndromes involving behavior, language, and motor function. The main syndromes encompassed by the clinical term Frontotemporal dementia are behavioral variant of Frontotemporal dementia (bvFTD), non-fluent variant primary progressive aphasia (nfvPPA) and semantic variant primary progressive aphasia (svPPA).

The FTLD syndromes share similar pathologic substrates but their clinical expression is markedly different and reflects selective injury of certain areas of the brain, which leads to diverse signs and symptoms. Specific atrophy patterns evident on structural images have been the basis of current research in FTLD and recent research shows that imaging has prognostic implications [2]. BvFTD is associated with an early change in personality and behavior. It is associated with grey matter atrophy in the frontal and temporal lobes, in particular the ventromedial frontal cortex, the posterior orbital regions, the insula bilaterally, and the anterior cingulate cortex. NfvPPA presents with non-fluent speech and language. It is characterized anatomically by left perisylvian atrophy, in particular, atrophy of the left frontal operculum (Broca areas 44, 45 and 47). SvPPA is a disorder with loss of the semantic knowledge of words [3].

In a field that had little to offer in terms of disease modification, there are now clinical trials of protein specific treatments. Treatment requires early diagnosis because reversal of disease is unlikely. At present discrimination of the different degenerative conditions and clarification of their clinical characterization and pathogenesis is also necessary to permit focus allocation of financial resources. In fact behavioral disturbances that are more prominent in patients with Frontotemporal dementia may require allocation of recourses for special care. In the diagnostic process, especially the differential diagnosis of FTLD, neuroimaging provides a particularly useful tool. In fact, the clinical evaluation of some functions may not be possible due to the lack of motivation of FTLD patients. Moreover, the typical tendency of FTLD to impoverishment of language, or even to mutism, leads to a decline in performance that cannot be interpreted unequivocally as a true impairment of these functions.

A combination of clinical and neuroimaging evaluations can maximize the accuracy of the diagnostic process. Structural imaging based on magnetic resonance is an integral part of the clinical assessment of patients with suspected Frontotemporal dementia. Imaging tools may provide information which partially overlaps between these different diseases, but with careful selection, these tools can add value to the diagnostic process.
Our aim is to assess the differential diagnosis of Frontotemporal Dementia with the use of visual rating scales establishing thus a cost effective diagnostic tool. While no structural imaging feature has perfect sensitivity and specificity for a given diagnosis, there are a number of imaging characteristics which give a positive predictive value to help narrow the differential diagnosis.
Methods and materials

Brain MRI exams of 65 patients (54.5% males and 45.5% females) were evaluated with different subtypes of Frontotemporal dementia (behavioral variant n=41, semantic dementia n=16, progressive non fluent aphasia n=8). Mean age (±SD) was 65.9 (±10.9) years, mean age at first evaluation 66.1(±10.9), mean disease duration was 3.4 (±2.2) years and educational level, as expressed with school years was 11.1 (±4.3). 96.8% of the population were right handed. A population of 40 controls, matched for age and educational level, was also assessed. Double blinded visual evaluation in order to assure intra-rater and inter-rater agreement, was performed by two trained neuroradiologists and the clinical diagnosis was set by a neurologist with specific interest in dementia. Disease duration and MMSE score were also evaluated.

The rating scales used were:

**Visual scales regarding specific regions** (dorsofrontal, orbitofrontal, anterior cingulate, anterior temporal, insula, lateral temporal, entorhinal, perirhinal and anterior fusiform cortex) according to a rating scale suggested by Davies et al [4]. Both hemispheres were evaluated separately.

**Pasquier rating scale for Global Cortical Atrophy (GCA) evaluation** which as reported in the literature presents strong correlation with the severity of Alzheimer's disease and MCI. Global volume loss without focal lobar atrophy is a common and non-specific finding on structural MRI studies in normal aging and dementia. Visual rating of cortical atrophy can be easily performed using a four point (0-3) Pasquier scale based on the width of the sulci and the volume of the gyri [5].

**Scheltens rating scale for Medial Temporal lobe Atrophy (MTLA) evaluation**, which can be used as a criterion in the clinical diagnosis of AD [6-8]. The five point Scheltens scale considering the width of the choroid fissure, temporal horn and the volume of the hippocampus, is an established rating scale for the assessment of the medial temporal lobe, which correlates well with histopathology and volumetric measurements.

**Fasekas White Matter Changes Scale**: as an easily applicable and highly reproducible four-point rating scale it is widely used in clinical practice and corresponds well with more detailed rating scales and histopathology, representing an important marker of vascular dementia [9]. Hyperintensities in cerebral white matter on T2-weighted or FLAIR imaging and less prominently on T1-weighted imaging, are more likely to be vascular in origin. Confluence of hyperintensities in at least two regions, and the beginning of confluence of hyperintensities in a further two regions is considered to represent the involvement of at least a quarter of the total white matter and is sufficient to assume small vessel disease is the cause of vascular cognitive impairment or vascular dementia. However, even in cases of extensive white matter hyperintensities, the existence of mixed pathology should be considered, although it may be difficult to confirm or refute.
Koedam rating scale for Posterior Cortical Atrophy evaluation involving the parietal/occipital cortex is usually the result of underlying AD pathology. Visual rating of posterior atrophy in combination with MTL atrophy rating has been reported to help discriminate AD from Frontotemporal dementia with a sensitivity of 73% and a specificity of 87% [10].

Controls had a negative history of neurological disease and no detectable cognitive deficit. All had MMSE administered, and were judged not to be suffering from dementia by a neurologist involved in the evaluation of the patients.

Written informed consent was obtained from both cases and controls or their primary caregivers. The study was approved by the ethics committee of our hospital.

Statistical analysis

Statistical analyses were carried out with IBM SPSS v. 17.0. Descriptive statistics were used. Cohen's kappa was calculated in order to assess inter-rater agreement. Analysis of variance (ANOVA) was used for assessing difference of mean values between diagnosis subgroups. The critical level for statistical significance was set at 0.05 for all tests.
Results

Corresponding analyses between disease groups gave significant differences between patients with bvFTD versus patients with svPPA in the orbitofrontal cortex (2.44 ±1.1 vs. 1.9±1; p=0.009) and anterior cingulate cortex (for right: 2.1±0.9 vs. 1.3±1, p=0.004 and for left: 2±0.9 vs. 1.1±0.8, p=0.003).

Anterior temporal atrophy was significant in patients with semantic variant. The semantic dementia variant had a characteristic pattern of loss, typically left rather than right involving the anterior temporal pole (fig 1). These atrophy patterns correlate well with quantitative MRI methods, such as voxel based morphometry (VBM), and with pathological studies, as reported in the literature. Semantic dementia is a clinical variant of Frontotemporal lobar degeneration (FTLD) characterized by progressive deterioration of semantic memory with relative sparing of other cognitive functions. It is associated with mainly left anterior temporal atrophy, and is also referred to as "left-temporal lobe variant" of FTLD. Recently, patients with mainly right-sided atrophy, or "right-temporal lobe variant" (RTLV), have been described. In our study one patient manifested right temporal atrophy. Left-predominant cases which almost entirely represent in our study, manifest as a fluent anomic aphasia, whereas patients with predominantly right anterior temporal atrophy manifest with a behavioral syndrome characterized by a flat effect, emotional blunting, and alterations in social conduct plus deficits in empathy and inability to recognize people’s emotions [11-14].

The svPPA versus bvFTD discrimination was based on the temporal lobe being atrophic in the former and the anterior cingulate in the latter, in keeping in accordance with their role in semantics and social cognition

Atrophy of the left hippocampus gave significant differences versus controls in patients with semantic and progressive non fluent aphasia (nfvPPA) [15-19]. Patients with nfvPPA also presented significant atrophy in the insular cortex versus controls (figure 2). NfvPPA is a disorder of expressive language and speech production and therefore characterized anatomically by left insular atrophy [20].

Brain morphology was constantly characterized in FTLD patients by atrophy of the anterior sections of the temporal and frontal lobes. BvFTD was associated with atrophy in the dorsal frontal cortex, the orbital frontal regions, the insula and the anterior cingulate cortex (figure 3). These regions are components of the emotional processing systems of the brain, so that their involvement in Frontotemporal dementia explains the unique behavioral symptoms seen in that disorder [20].

One of the most typical features of FTLD is asymmetry. Greater asymmetry was observed in patients with behavioral variant (figure 3). A minority of our patients presented with symmetric Frontotemporal and medial temporal atrophy, of a more severe degree compared to those patients with an asymmetric involvement. The asymmetry was
more prominent in the orbito-frontal cortex, the dorso-frontal, the insula, the anterior hippocampus, the entorhinal cortex, the perirhinal cortex and the anterior fusiform.

All the patients with symmetric atrophy had an early onset of the disease and presented greater atrophy in the frontal and temporal regions. Moreover, medial temporal atrophy was absent, or rather minor in the asymmetric, and markedly greater in symmetric patients. Global values of Frontotemporal, medial temporal and overall atrophy indicate significantly greater atrophy in symmetric patients. In patients with asymmetric disease, only the left frontal and temporal regions were affected.
**Fig. 1:** Figure 1. Coronal T1WI of a 62 year old female patient with semantic dementia presenting significant left temporal, anterior fusiform and hippocampal atrophy.

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**Fig. 2:** Figure 2. Coronal T1WI of a 64 year old female patient with non-fluent variant primary progressive aphasia (nfvPPA) presenting significant left insular and predominantly left hippocampal atrophy

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**Fig. 3:** Figure 3. Coronal T1WI MRI of a 72 year old male patient with behavioral variant of Frontotemporal dementia (bvFTD) presenting atrophy of the anterior sections of the temporal and frontal lobes. The posterior regions are preserved. Asymmetry in the above regions is also observed.

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Conclusion

FTLD is a clinically and pathologically heterogeneous spectrum of disorders. Clinical diagnosis of the cause of cognitive complaints can be difficult. Nonetheless accurate and timely diagnosis is increasingly important to guide management and to provide appropriate information and support. In the last few years, neuroimaging has contributed to the phenotypic characterization of these patients. Structural imaging in cognitive cases can provide easily accessible, clinically useful information. It is the primary neuroimaging technique of choice in clinical practice to support the clinical diagnosis of dementia.

Visual rating scales can become a diagnostic tool in the differential diagnosis of patients with FTLD and can be used in alternative to highly technical methods of quantification. The disadvantages of the rating approach are obvious, since it will not give precise volumes. Rating is also prone to sampling error in that only one view of a structure is assessed. Furthermore rating can be criticized for lacking objectivity although this can be improved by rigorous blinding.

The syndrome-specific atrophy patterns are useful for diagnosing the different syndromes. The pattern of atrophy might be more informative and discriminative between the different diseases and also superior to the single region approach, since atrophy of single regions may overlap in the different diagnostic groups. This approach may be effective when dealing with single cases or small groups in combination with clinical assessment.
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