Diagnosis of Fronto Temporal Lobar Degenerations (FTLD)

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Disclosure

None
Learning objectives

• Clarify the complex FTLD scenario

• Provide basic knowledge of these neurodegenerative disorders

• Present the current neuropathological and molecular data of FTLD

• Describe the clinical features of the different types of FTLD

• Give to the clinical neurologist a diagnostic approach in front of an clinical case evocative of FTLD spectrum
Key message

• FTLD: spectrum of neurodegenerative disorders characterized by a degeneration of the frontal and anterior temporal lobe; complex and heterogeneous diseases

• One of the most common forms of presenile dementia

• Several different proteins aggregates: tau, TDP-43, FUS...

• Many genes (MAPT, C9ORF72, GRN, VCP...), explaining 50-60% of familial FTLD

• Wide spectrum of disorders: bvFTD, nfvPPA, svPPA, PSP, CBDS, FTLD-ALS...

• Diagnostic approach: clinical phenotype, family history, location of atrophy on MRI, exclusion of treatable neurological and psychiatric conditions

• Consider genetic testing if family history or certain clinical features
OUTLINE

Introduction

FTLD proteotypes / Neuropathology

FTLD genotypes / Genetics

FTLD phenotypes / Clinical description:
  Major phenotypes
  Related phenotypes

Diagnostic approach of FTLD syndromes
Introduction (1)

• FTLD : spectrum of neurodegenerative disorders characterized by a degeneration primarily located in the frontal and anterior temporal lobe

• One of the most common forms of presenile dementia

• Variability and overlapping in clinical, genetic and histopathologic features

• Symptoms ranging from behavioral and executive disturbances to different language disorders +/- motor neuron disorders or parkinsonism

• Different proteins detected in aggregates : Tau, TAR-DNA-Binding Protein-43 (TDP-43), Fused in Sarcoma (FUS) and other ubiquitin proteins (U)

• Many causative genes described, mostly MAPT, C9Orf72, GRN, VCP....
• FTLD : reserved for patients with clinical presentations of FTD and identification of an FTD-causing mutation or histopathologic evidence of FTD
• FrontoTemporal Dementia (FTD) : refers to one of several clinical subtypes, defined by the hallmark patterns of symptoms and signs observed
• Syndromes assigned to the FTLD spectrum (Seltman and Matthews 2012):
  • the 3 types FTD :
    • behavioral variant of frontotemporal dementia (bvFTD)
    • semantic and non-fluent variant of primary progressive aphasia (svPPA and nfvPPA)
  • FTD with motor neuron disease (FTD-MND), mainly ALS (FTD-ALS)
  • Progressive supranuclear palsy (PSP)
  • Corticobasal syndrome (CBS)
FTLD proteotypes / Neuropathology

- FTLD characterized by proteinaceous intracellular aggregates in the brain

- Two pathologic categories of FTLD according to the protein observed:
  - microtubule-associated protein Tau in about 40% of FTLD
  - ubiquitin proteins in about 60% of FTLD; among them:
    - transactive response (TAR) DNA binding protein 43 (TDP-43) in 80%
    - fused in sarcoma protein (FUS) in 10%

- Each FTLD pathological subtype can cause several FTD syndromes

Molecular and genetic classification of FTLD
Adapted from Li et al., 2015
FTLD-tau

• Tau protein stabilizes axonal microtubules by interacting with tubulin

• Encoded by the microtubule-associated protein tau (MAPT) gene → 6 tau isoforms produced by alternative splicing, different expressions

• MAPT mutations consistently associated with tau pathology

• Tau becomes aberrantly hyperphosphorylated, dissociates from microtubules, and forms aggregates within neurons and glia

• Among FTLD cases, different electrophoretic profiles (Noble et al., 2013):
  • phosphorylated 3R isoforms (3R tauopathy) → Pick’s disease (PiD)
  • phosphorylated 4R isoforms (4R tauopathy) → PSP, CBD
FTLD-TDP

- TARDNA-binding protein 43 (TDP-43) : major ubiquitinated protein associated with tau-negative FTLD

- TDP-43 encoded by the TARDBP gene

- About 50% of FTLD patients have aggregates positive for TDP-43

- TDP-43 subclassified according to patterns of TDP-43-containing neuronal cytoplasmic inclusions and dystrophic neurites in diseased neurons

- 4 subtypes of FTLD-TDP, according to morphological appearance of inclusions and lesions distribution: types A to D (Mackenzie et al., 2010)
FTLD-FUS

- Fused in sarcoma (FUS) : RNA-binding protein involved in splicing and nuclear export of mRNA
- FUS mutations mainly associated with bvFTD and FTD-MND (and ALS alone)
- Specific phenotype related to sporadic FTLD-FUS :
  - young onset (22–46 years)
  - prominent caudate atrophy
  - unique phenotypic features : marked obsessiveness, social withdrawal, hyperorality, stimulus-bound repetitive, ritualistic behaviours
  - cognitive profile : subcortical executive dysfunction in the absence of cortical language, perceptual and praxis impairments
Correlations phenotype/proteotype

• **bv-FTD** : all molecular subtypes

• **nfv-PPA** (PNFA) : around 85% show 4R or 3R tau pathology

• **CBDS** : mainly 4R tau pathology

• **PSP** : 4R tau pathology

• **sv-PPA** (SD) : 90% of **TDP-43** (type C)

• **FTD–ALS** : almost always **TDP-43** pathology (usually type B)

Adapted from Rabinovici & Miller, 2010
FTLD genotypes / Genetics

- Positive family history observed in 40–50% of the FTLD
- About 10-15% show a clear autosomal dominant inheritance pattern
- In familial FTLD, genes associated with homogenous pathological signatures
- Many genes identified, currently explaining 50-60% of familial FTLD
- FTLD-tau: associated with MAPT mutations
- FTLD-TDP: very diverse mutations, 4 main molecular etiologies
  - Mutations in chromosome 9 open reading frame 72 gene (C9orf72)
  - Mutations in the progranulin gene (GRN)
  - Mutations in valosin-containing protein gene (VCP) and TAR DNA-binding protein gene (TARDBP)
Genetics of FTLD

- **MAPT, GRN and C9ORF72 mutations**: at least 17% of familial FTLD
  - MAPT $\rightarrow$ mainly bvFTD, PPA; parkinsonism; no ALS
  - C9ORF 72 $\rightarrow$ FTD, FTD-ALS and ALS
  - GRN $\rightarrow$ parkinsomism in 40%; bvFTD in 60% of cases; PPA, CBS; low plasma level
- **TARDBP and FUS genes mutations**: number of cases of bv-FTD, FTD-ALS, ...
- **Rare mutations in other genes encoding**:
  - Valosin Containing Protein (VCP) $\rightarrow$ Inclusion body myopathy with Paget’s disease of bone and frontotemporal dementia (IBMPFD)
  - Charged Multivesicular Body Protein2B (CHMP2B) $\rightarrow$ Usually bvFTD, also more global loss of cognition, parkinsonism, dystonia, and myoclonus
  - Ubiquilin-2 (UBQLN2) $\rightarrow$ described in FTD-MND, dominant X-linked
  - Sequestosoma (SQSTM1) and other genes mutations
Genetic associations in FTLD and ALS

- **FTLD-Tau**: 45% of all FTLD; mutations in *MAPT* (sole known cause of hereditary forms)
- **FTLD-TDP**: 50% of all FTLD; hereditary forms associated with pathogenic mutations in *GRN*, *C9orf72*, *TARDBP* and *VCP* and other genes
- **FTLD-ALS/ALS** cases more associated with *C9orf72* and *TARDBP*; less commonly linked to *VCP* and rarely *GRN*
- **TARDBP** rarely associated with FTLD without co-morbid ALS
- Very rare cases of **FTLD** (other) associated with pathogenic mutations in *CHMP2B* and FTLD-U neuropathology

Irwin et al. 2015
FTLD phenotypes / Clinical description

Major phenotypes
behavioral variant FTD (bvFTD)

- Represents more than 50% of FTLD cases and the most heritable form
- Onset typically before the age of 65; male predominance
- Changes in personality and behavior, mixture of apathy and disinhibition
- Repetitive motor behaviors, changes in eating behavior, hyperorality
- Poor judgment, distractibility, loss of planning ability, perseverative errors
- Deficits on frontal/executive tasks (dorsolateral prefrontal cortex)
- Attention and working memory impaired; episodic memory relatively spared
- Semantic loss, aphasia (often adynamic)
- Parkinsonism, oculomotor control problems, or motor neuron disease
1 – bvFTD

• Neuroimaging → frontal atrophy, hypometabolism and hypoperfusion
• Earliest changes: anterior cingulate, orbital frontal, frontoinsular cortices
• Dorsolateral prefrontal cortex often involved
• Region of greatest atrophy correlates with clinical phenotype:
  • dorsomedial frontal → apathy and aberrant motor behaviour
  • orbitofrontal → disinhibition

Seeley, 2019
2 – Non Fluent/aagrammatic variant Primary Progressive Aphasia (nfvPPA)

- **Agrammatism** and motor speech deficits
- **Apraxia of speech**: difficulty initiating, slow rate of speech, incorrect sequencing of phonemes
- Phonemic paraphasic errors and mild anomia (without semantic loss)
- Comprehension: spared for single words and simple sentences, impaired for complex sentences
- Deficits in working memory and executive function; episodic memory, visuospatial function spared
- Supranuclear gaze palsy, parkinsonism and limb apraxia → frequent association with CBD and PSP
- Neuroimaging: dominant inferior frontal lobe (including Broca areas), left frontal operculum, premotor and supplementary motor areas and anterior insula, superior temporal gyrus

Mesulam, Ann Neurol, 2001
3 – Semantic variant PPA (svPPA)

- Atrophy of the medial and lateral portions of the anterior temporal lobes, usually more on the left
- Core features: Anomia and single-word comprehension deficits (Gorno-Tempini et al., 2011)
- Progressive loss of ‘semantic’ knowledge about words, loss of word meaning, objects and concepts → multimodal agnosia with time
- Fluent aphasia with impoverished speech content and semantic paraphasic errors
- Intact grammar, prosody and motor speech
- Impaired confrontation naming and category fluency, single-word comprehension
- Spared episodic memory, spatial abilities and executive functions
- Right temporal involvement → behavioral syndrome that overlaps with bvFTD
Patterns of brain atrophy in FTD syndromes
Elahi & Miller, 2017
FTLD phenotypes / Clinical description

Related phenotypes (Motor FTD syndromes)
1 – FTD with Motor Neuron Disease (MND)

- ALS: most common form of presentation of MND

- Familiar and sporadic cases of ALS may have frontal lobe dysfunctions: personality and behavior changes, planning, organization and language dysfunction...

- About 40% of ALS patients show symptoms of FTD

- About 50% of FTD patients have ALS-like symptoms

- ALS symptoms may precede, occur simultaneously, or follow the signs and symptoms of FTD

- Most common symptomatology: cognitive change first, followed by weakness
2 – FTD overlap syndromes

• **Cortico basal degeneration syndrome : CBDS**
  • extrapyramidal symptoms with progressive asymmetric rigidity and dystonia
  • limb apraxia, cortical sensory loss, alien limb syndrome, hemispatial neglect and myoclonus
  • executive and visuospatial dysfunction
  • frequent combined picture, often associated with nfvPPA and behavioral disorders in the last stages of the disease

• **Progressive Supranuclear Palsy syndrome : PSPS**
  • primarily postural instability, axial predominant parkinsonism, profound retropulsion
  • supranuclear gaze palsies
  • dysarthria, apraxia of speech, dysphagia and pseudobulbar affect
  • executive dysfunction, psychomotor slowing and poor working memory
Summary
Molecular, genetic and clinical correlations in FTLD

From Li et al., 2015

Adapted from Elahi & Miller, 2017
Diagnostic approach

• Based on clinical symptoms, family history (intrafamilial phenotype heterogeneity), location of atrophy

• MRI to evaluate pattern of atrophy and non degenerative lesions

• Exclude treatable conditions that can mimic FTLD: metabolic nutritional conditions, CNS infections, substance abuse, vascular disease, heavy metal toxicity, primary neoplastic and paraneoplastic conditions...

• Exclude primary psychiatric disorder (major depression or bipolar affective disorder): little progression over time and no FT atrophy on MRI

• Amyloid biomarkers (CSF or PET) if AD is included in the differential diagnosis

• Next challenge: predict the underlying histopathology (probabilistic correlations)
Consider genetic testing for bvFTD and FTLD-ALS patients.

Algorythm for genetic testing based on 4 criteria:

- Presence of ALS in the patient himself or in one of his relatives
- Age at onset of FTLD
- Level of progranulin in plasma
- Other disorders present in the patient or associated in his family

Diagram:

- Familial FTLD
  - Multisystem proteinopathy
    - FTLD
    - PDB
    - Myopathy
    - ALS
  - Progranulin plasmatic level
    - Low PGRN
    - Normal C9ORF72
      - No mutation
        - T2-WM hypersintensities
          - CSF1R
          - TREM2
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