SPECTRUM OF FRONTOTEMPORAL DEMENTIA

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What is Frontotemporal Dementia (FTD)?

- It is a heterogeneous disorder with distinct clinical phenotypes
- Group of clinical syndromes linked to underlying neuronal loss in frontal and temporal lobes
- Associated with multiple neuropathological and genetic entities seen in both familial and sporadic forms
- It often begins in 5^{th}-7^{th} decade of life and found more commonly in men than woman. Family history of dementia is commonly linked to FTD with Autosomal Dominant inheritance of about 10-20 % of all the cases

PATHOGENESIS:

Gross pathologic hallmark - focal atrophy of the frontal, insular and temporal cortex on neuroimaging. Atrophy begins focally in one hemisphere before spreading to other anatomically interconnected cortical and subcortical regions.

Histological and Genetic evidence:

Proteins:

- Tau
- TDP-43
- FUS

Genes:

- C9ORF72
- GRN
- MAPT

CLINICAL FEATURES:

Progressive changes in Frontotemporal Lobar degeneration with prominent changes in social behavior, personality changes and language deficiencies.

Behavioral:

- lack of personal hygiene and grooming
- Impulsive behaviors and disinhibition
- Lack of executive control
- Hyperorality
- Inappropriate social conduct

Language:

- Difficulty in comprehension or production of speech

HISTOLOGY:

Microscopic findings across all patients with Frontotemporal Lobar degeneration (FTLD) includes:

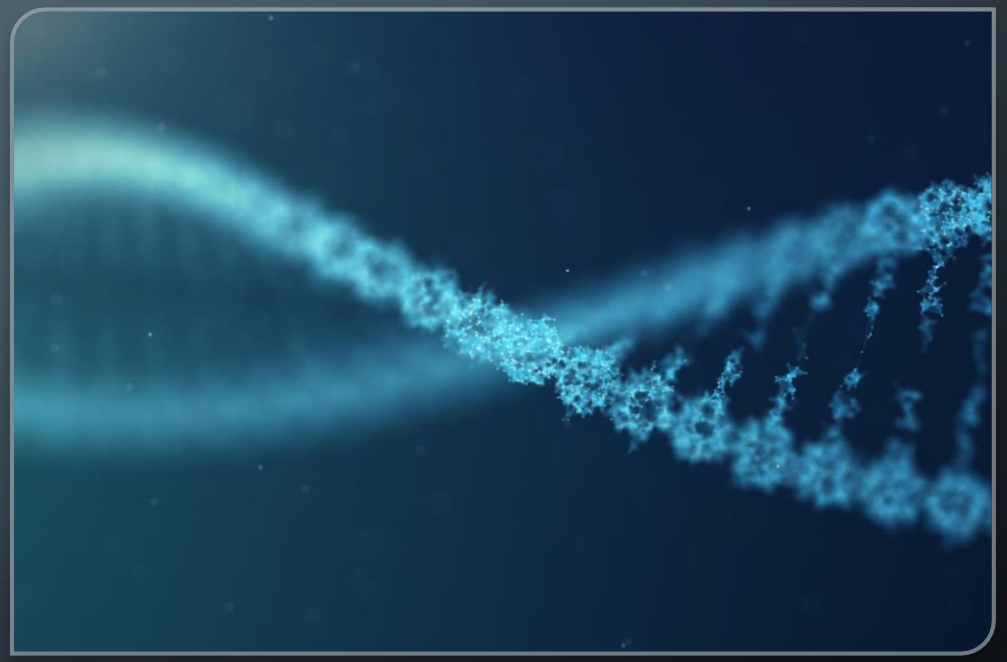
- Gliosis, microvacoulation and neuronal loss.
- Disease subtypes are associated to different aggregated protein composition containing either Tau, TDP-43 or FSU inclusions in the neurons and glia.

- Tau is a microtubule associated protein presenting as intracytoplasmic inclusions of rounded bodies known as Pick bodies or as neurofibrillary tangle-like structures
- TDP-43 (transactive response DNA-binding protein) is present as ubiquitinated neuronal intracytoplasmic/intranuclear inclusions
- FUS (fused in sarcoma) also known as TLS (translocation in liposarcoma) also present as cytoplasmic inclusion bodies. Mutations in FUS may have associations with Amyotrophic Lateral Sclerosis (ALS)

GENETICS

Three major genes identified for FTLD include:

C9ORF72, GRN and MAPT



GENES AND ITS ASSOCIATIONS

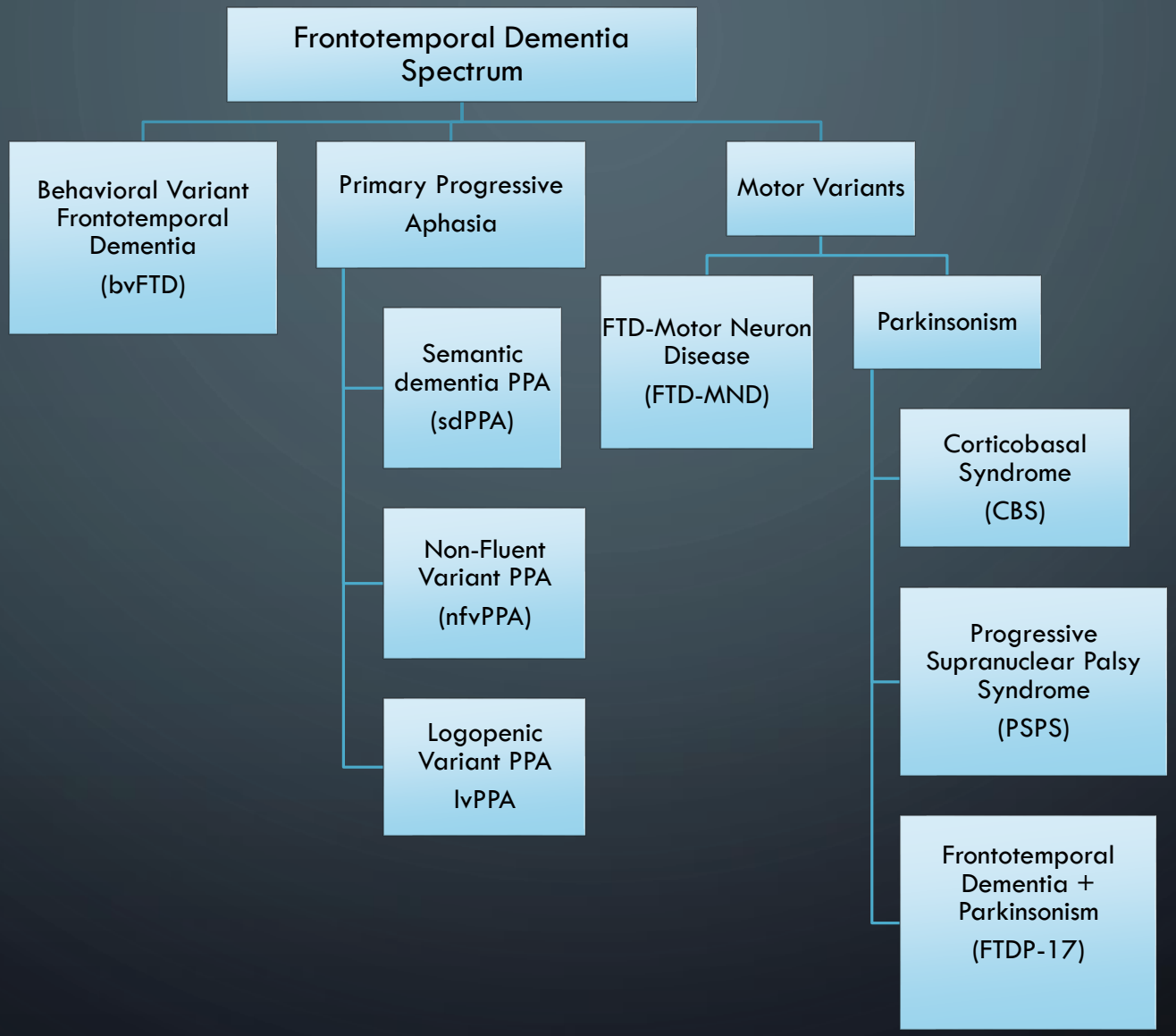
- C9ORF72 is a protein abundantly found in the brain and spinal cord that controls movement (motor neurons). The expansion of noncoding exons of C9ORF72 on chromosome 9 presents with bvFTD for familial or sporadic forms. C9ORF72 mutations have also been linked with ALS causing muscle weakness, loss of muscle mass and inability to control movements.

- GRN (granulin) mutations are found in the coding sequence encoding for progranulin protein. Progranulin is a growth factor and binds TNF receptors which participates in regulating tissue repair, survival and inflammation. Likely mechanism of progranulin dysfunction includes lysosomal dysfunction and enhanced neuroinflammation.

- MAPT (Microtubule-Associated Protein Tau) makes the protein Tau. It is involved in assembly and stabilizing the microtubule. Mutations leads to changes in the alternative splicing of tau and causing a loss of function and alternating the microtubule binding.

- Both GRN and MAPT mutations have been associated with parkinsonian features.

TYPES OF FTD VARIANTS



Diagnostic Behavior and Language Clinical Features

bvFTD	sdPPA	nfvPPA	lvPPA
Behavior:			
- Decline in personal hygiene. - Disinhibition, Distractibility and impersistence. - Repetitive stereotype behavior - Hyperorality, inappropriate sexual behavior. - Dietary changes.	- Loss of sympathy and empathy - Impaired recognition of familiar faces/objects	- Memory is intact - Limb and orofacial apraxia	
* Relatively preserved episodic memory and visuospatial function in early stages	* Preserved single word repetition w/fluent speech, matching and drawing	* Preserved single word comprehension and object knowledge	* Preserved single word comprehension w/o agrammatism. Pt retrieves right word and are well-articulated, (i.e., 'Coptain' rather 'Captain').
Language:			
- Echolalia- vocal repetition. - Perseveration- repetition of particular response. - Mutism.	- Impaired naming comprehension - Semantic paraphasia- loss of ability to speak correctly - fluent speech w/Loss of word meaning	- non-fluent (Broca) speech - Agrammatism - Impaired sentence comprehension and distorted speech sound (i.e 'capititan' rather 'captain'). - Slow speech production	- Frequent word finding pauses. - Impaired comprehension of longer sentences.

FTD- MOTOR VARIANTS

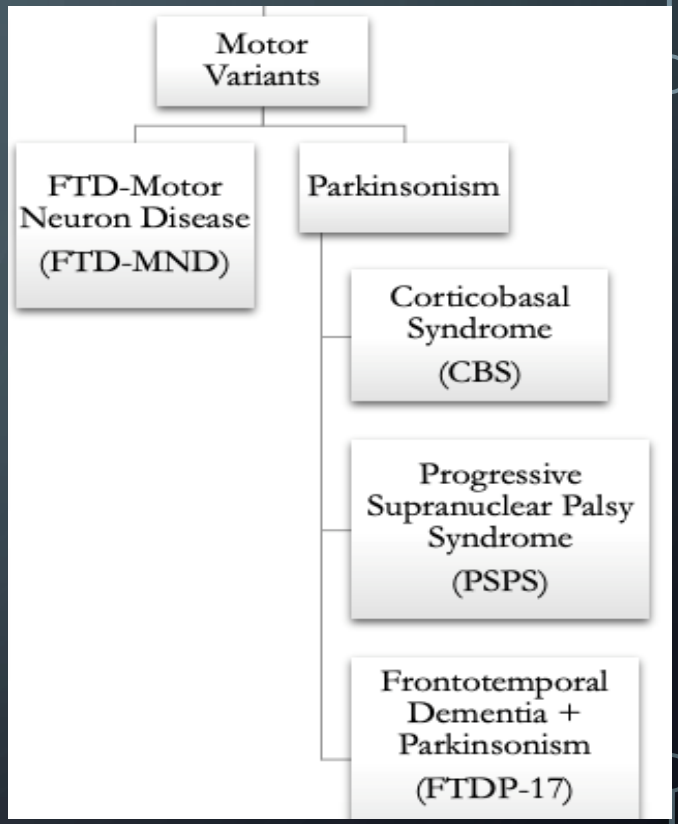
Any of the FTD can also develop concurrent motor neuron disease (MND) or an atypical parkinsonian disorder.

- Three subtypes of atypical parkinsonian disorder:

  1). The corticobasal syndrome (CBS)

  2). Progressive supranuclear palsy syndrome (PSPS)

  3). Frontotemporal Dementia + Parkinsonism (FTDP-17)



Some patients may develop motor neuron disease (MND) in the form of ALS (weakness, wasting and fasciculations of the muscles). The presence of ALS symptoms augments the FTLD disease severity.

ATYPICAL PARKINSONISM

CBS- progressive dementia-movement disorder. Severe degeneration in substantia nigra and striatopallidum.

Asymmetrical onset of:

- Rigidity, dystonia, myoclonus, and apraxia of one limb
- Associated with Alien limb phenomena
  - limb exhibits unintended motor actions such as grasping, groping, drifting or undoing
- Bilateral involvement leads to
  - dysarthria, slow gait, action tremor and frontal-predominant dementia

ATYPICAL PARKINSONISM CONTINUED…

PSP-S (aka Steele-Richardson Disease)- involves the brainstem, basal ganglia. Clinically, it begins with falls and executive or subtle personality changes:

- Mental rigidity, impulsivity or apathy.
- Oculomotor syndrome- vertical>horizontal supranuclear gaze palsy.
- Stiff, unstable posture with hyperextension of the neck and slow jerky toppling gait are characteristic.

FTDP-17 - FTD and Parkinsonism linked on chromosome 17 with mutations in tau protein. Familial Autosomal Dominant inheritance.

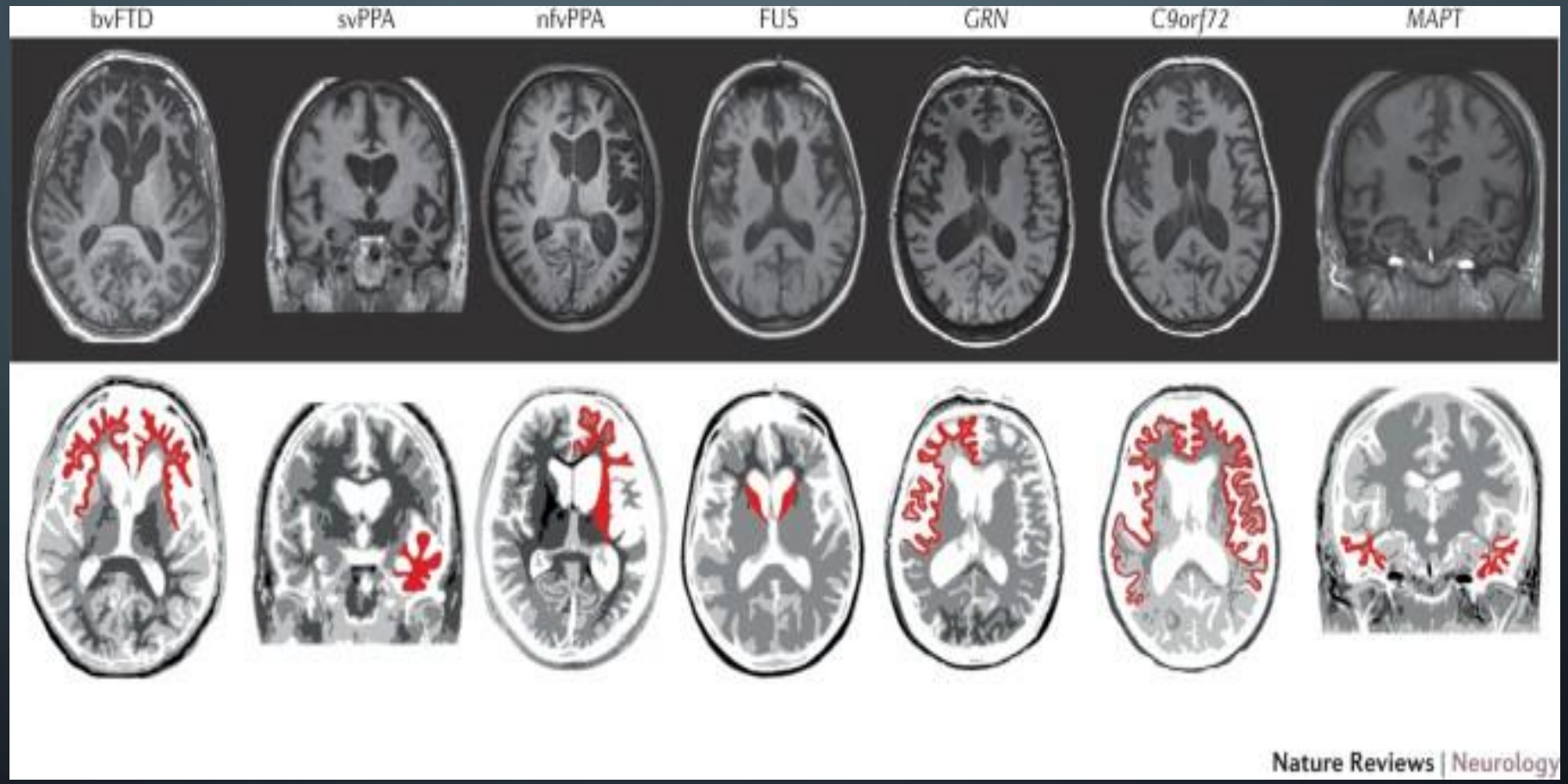
- Three major clinical features include:
  - 1. Behavioral disturbances,
  - 2. Cognitive impairment
  - 3. Parkinsonism.

FTD-MND

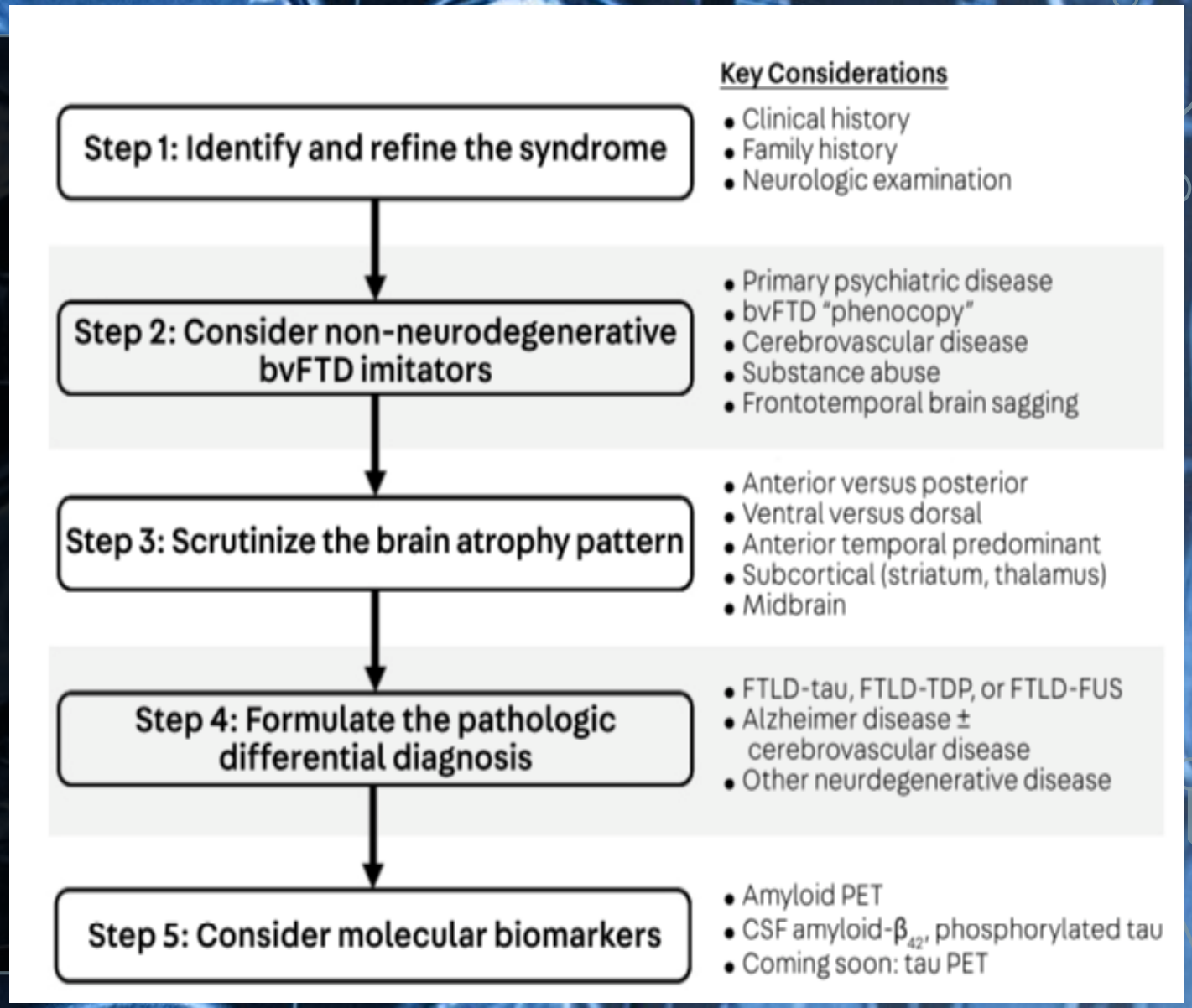
- Typically begins with changes in behavior, cognition and/or language with prominent psychiatric symptoms (hallucinations/delusions). As the disease progresses, within 1-2 years, there is classical features of MND involving upper and lower limb wasting, weakness and fasciculations. As well as dysarthria, dysphagia, respiratory failure and spasticity.

- bvFTD has been commonly been linked with MND (Amyotrophic lateral sclerosis) due to mutations in C9ORF72

LOCALIZED ATROPHY



DIAGNOSTIC APPROACH



DIAGNOSTIC SCREENINGS:

- Structural Brain MRI- to compare brain atrophy and abnormalities
- Brain FDG PET and Perfusion SPECT Scan- hypometabolism and hypoperfusion are typically seen in frontal and anterior temporal lobes
- CSF biomarkers: T-tau and P-Tau – used to diagnose AD as less likely when doubt exists
- Genetic Screening- of the known gene mutations linked to FTD
- DTI (Diffusion Tensor Imaging)- MRI technique used to visualize water diffusion in the white matter. White matter damage is an early marker for FTD
- Resting-state functional MRI- checks for loss of function connectivity involving brain areas that process emotions, behavior and interpersonal experiences
- ASI (Arterial Spin Labeling)- MRI techniques used to measure cerebral blood flow
- EEG (Electroencephalography) – measures physiological functionality of the brain

DIFFERENTIALS:

- Alzheimer's Disease
- Huntington Disease
- Parkinson Disease
- Prion Disease
- Spinal muscular atrophy
- Motor Neuron Diseases

TREATMENT AND MANAGEMENT

No disease-modifying therapies are available. Treatment is focused on the most disruptive or targetable behaviors.

Pharmacotherapy and Non- Pharmacotherapy

- Antidepressants (SSRIs)and Atypical Antipsychotics- to treat social inhibition and impulsive behavior. (i.e citalopram, escitalopram, venlafaxine, quetiapine or risperidone…).
- Alzheimer's Medications- to improve behavioral and cognitive symptoms (i.e Rivastigmine, Galantamine…)
- Speech-language pathologist- to determine best tools and strategies to use during language deficits.
- Physical and Occupational Therapist- to improve motor functions
- Family counseling- to help families understand the disease and provide care for their loved ones affected by the disease.

PROGNOSIS:

The outcome for people with Frontotemporal Dementia is poor. The disease progresses steadily and rapidly. Average mean duration of symptoms from onset until death is 8 years but can vary from less than 2 years to more than 20 years in others depending on the rate of progression.

Eventually some individuals with FTD will need 24-hour care and monitoring at home or in an institutionalized care setting.

FUTURE GOAL

- Genetic mutations and Proteins are being investigated further.
- Neurofilament light chain (NFL)- new CSF and serum biomarker is being studied as potential diagnosis of FTD. Markers suggest presence of neurodegeneration and is likely found in FTD and Alzheimer's Disease. It is significantly increased more in FTD.
- Identify and test possible new drugs and other treatments targeting FTD.

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