AGING, DEMENTIA, COGNITIVE AND BEHAVIOURAL NEUROLOGY

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This Case-based course will provide the participants with a clinical approach to assess and diagnose patients with atypical, non-Alzheimer's dementia including frontotemporal dementia (FTD), Lewy body dementia, and dementia associated with movement disorders such as Huntington's disease, progressive supranuclear palsy (PSP), corticobasal syndrome (CBS) (mixed pathology) or corticobasal degeneration (tau-related) and spinocerebellar ataxia. The approach to diagnosis, like always, should involve a detailed history to localize the lesion ("Where is it?") and generate a differential diagnosis ("What is it?"). In behavioural neurology a good detailed collateral history from a spouse of friend is vital – is the problem an amnesic and language issue as found in Alzheimer's disease or an insidious behavioural change as often found in FTD? The neurological examination is then designed to confirm or refute your possible diagnosis based upon the history (Figue 2). Various investigations such as morphological brain imaging (CT, MRI), functional brain imaging (fMRI, glucose/amyloid/tau PET imaging), CSF analysis including amyloid and tau ratios and genetic testing can then be used to support the clinical diagnosis (Figure 2)

In patients whose first and most prominent symptom is abnormal movement (hypokinetic & hyperkinetic) including vertical supranuclear gaze palsy in PSP, delayed latency of eye saccadic movement and alien limb phenomena in CBS, ataxia and an abnormal pull test in normal pressure hydrocephalous, and effortful abnormal speech in apraxia of speech, the clinician can perform specific bedside tests and maneuvers, which we will review. Although a detailed well-thought through neuro-cognitive assessment by an experience neuropsychologist is very helpful, these professionals often do not perform cognitive-motor tasks, or they may not be experienced with working with patients with movement disorders. To localize which cerebral regions are affected, we can perform some classical tests of motor sequencing, self-monitoring, and skilled learned movement processing (Table 1).

Table 1: Movement disorders associated with atypical dementia

Movement-related Symptom	Characteristics	Associated atypical dementia	Pitfalls/mimics/differential diagnosis
Limb apraxia	Skilled learned purposive movements are impaired	Corticobasal ganglionic degeneration, Diffuse Lewy Body Disease	--Slow/clumsy movements may be present in a number of disorders --Disconnection syndrome/stroke --Alzheimer Disease --Examiner may be too generous/forgiving
Motor sequencing abnormality	Fist-edge-palm (Luria 3-step hand command) , alternating hand closure	Any of the Parkinson-Plus	--ignore small gain of movements or decrement --patients who need to speak the sequence as they perform the task are probably impaired
Alien limb	Spontaneous elevation, intermanual conflict,	Corticobasal syndrome, can occur in stroke but usually non-progressive	--consider testing the leg as well as the arm! Draw an "S", kick a ball --Disconnection syndrome/stroke, any disorder causing limb apraxia
Impaired motor response inhibition	Abnormal antisaccade task or go-no go testing	Huntington Disease, all Parkinson-plus syndromes, FTD	--ensure errors are not due to deficient understanding or recall of the task
Combination of ALS, FTD and sometimes parkinsonism with mannerisms	Decreased arm swing, pull tests positive, mannerisms, wasting & fasciculations	ALS-FTD & parkinsonism (usually C9odrf72)	Videotape the examination including gait, eye movements and rapid movements as often the parkinsonism is missed

Anosognosia in Movement Disorders and Atypical dementia:
Anosognosia is seen in movement disorders and neurodegenerative disease. For example patients with Parkinson's disease are often aware of their limited activities of daily living and will score the Schwab & England activities of daily living scale accurately. However they are usually not aware of their soft voice and only become aware of the problem when they are ignored in company. In PSP patients are frequently blissfully unaware of their imbalance and walk with a narrow base in comparison to patients with cerebellar ataxia. PSP patients often pivot quickly on turning or launch themselves out of a chair with no regard to their safety (the "rocket sign"). Progressive neglect of the parkinsonian side is common in CBS with associated asterognosis & graphesthesia, stimulus-sensitive myoclonus, ideomotor apraxia and alien limb phenomena.

Frontotemporal dementia
FTD or frontotemporal lobar degeneration (FTLD), previously referred to as Pick's disease, was first described by Arnold Pick over 100 years ago. [1] Agrophilic globular neuronal cytoplasmic inclusions (Pick bodies) [2] are present in 20% of FTD [3], thus the term Pick's disease is used to describe FTD with Pick's pathology including Pick bodies. FTD, the second most common cause of dementia after Alzheimer's disease, represents 5-10% of all dementia and 10-20% cases under age 65. [4] Between 20% and 50% of patients have a family history and 10% have a clear autosomal dominant pattern of inheritance. [4, 5]
The diagnosis of FTD can be challenging due to a symptom overlap with Alzheimer's disease (short term memory problems, difficulty in performing visuospatial tasks, but social behaviours are spared), dementia with Lewy bodies (fluctuating course, visual hallucinations, parkinsonism and polyminimyoclonus), vascular dementia (stepwise progression, pseudobulbar palsy) and Huntington's disease (chorea and dementia). [11]
FTD is subdivided into a behavioural variant with disinhibition (bvFTD) (Table 2) and primary progressive aphasia (PPA) that includes subtypes of semantic dementia (semantic variant), progressive nonfluent aphasia (nonfluent/agrammatic variant) and logopenic variant with language dysfunction and variable behavioural change (Table 3).

Table 2: Diagnostic Criteria for bvFTD

Possible bvFTD – at least three of the following features must be present
1. Disinhibition
2. Apathy
3. Lack of Sympathy/empathy
4. Stereotypic/ritualistic behaviours
5. Change in dietary preferences
6. Frontal dysexecutive cognitive profile
Probable bvFTD – all of the following features must be present
1. Meet criteria for possible (as above)
2. Show functional disability/decline
3. Frontal and or temporal abnormalities on neuroimaging (MRI or PET)
Definite bvFTD – either 1 or 2 must be present
1. FTLD pathology or autopsy
2. Known pathogenic genetic mutation

Table 3: Diagnostic criteria for Primary Progressive Aphasia

1. Language disturbance is the most prominent clinical feature	
2. Language impairment is the cause of impairment in activities of daily living	
3. Aphasia should be the most prominent deficit at symptom onset and initial phases of disease	
4. No other condition explains the presentation	
A. PPA-sv (semantic variant) - both of following must be met	**B. PPA-nfv (agrammatic/non-fluent variant) – at least 1 of following must be met**
1. Poor confrontation naming (pictures/objects) particularly for low familiarity items	1. Grammatical errors and simplification in language production
2. Impaired single word comprehension	2. Effortful, halting speech with speech sound errors consistent with apraxia of speech
Plus at least 3 of following must be met	**Plus at least 3 of the following must be met**
• Poor object and/or person knowledge particularly for low frequency or low familiarity objects	• Impaired naming, especially action verbs
• Surface dyslexia	• Impaired comprehension of syntactically complex sentences
• Spared single word repetition	• Spared object recognition
• Spared motor speech, melody and phrase length	
Plus abnormal neuroimaging – especially anterior temporal lobe	**Plus abnormal neuroimaging – mainly left posterior fronto-insular cortices**
C. PPA-lv (logopenic variant) – both of following must be met	
• Impaired single word retrieval in spontaneous speech & confrontational naming	
• Impaired repetition of sentences and phrases	
• At least 3 of following must be met	
• Phonological errors is spontaneous speech & naming	
• Spared motor speech	
• Spared single word comprehension	
• Spared object comprehension	
Plus abnormal neuroimaging – predominant left posterior perisylvian or parietal	

New insights into FTD via genetic discoveries in Frontotemporal Dementia:

The discovery of various genes associated with FTD has led to significant insights into the molecular biology of the FTD. This is especially true of the identification of MAPT mutation in a number of FTD pedigrees in 1998 – these were named frontotemporal dementia and parkinsonism linked to chromosome 17 (FTDP-17) [6-10]. Mutations in microtubule-associated protein tau (*MAPT)*, granulin (*GRN)* and hexanucleotide expansion repeats in the open reading frame of chromosome 9 (*C9orf72)* are found in 60% of familial FTD cases (Figure 2). *C9orf72* mutations are the most common and accounts for 25% of patients. [14] Rarer mutations (<5%) occur in: valosin-containing protein (*VPC)*, chromatin-modifying 2B (*CHMP2B)*, TARDNA binding protein 43 encoding gene (*TARDP),* fused in sarcoma gene (*FUS),* integral membrane protein 2B *(ITM2B or BRI2)* [11,12] and tank-binding kinase 1 (*TBK1)* (Table 1) [13] and TATAbox binding protein (TBP) [14] (Figure 1). In individual patients there can be considerable overlap between the various clinical syndrome described above and this can lead to confusion. The clinician needs to keep in mind there is often a spectrum of disease in FTD with significant overlap with movement disorders such as CBD/CBS and PSP (Figure 1).

Figure 1: Overlap syndrome between Corticobasal syndrome, Frontotemporal dementia and Progressive Supranuclear Palsy

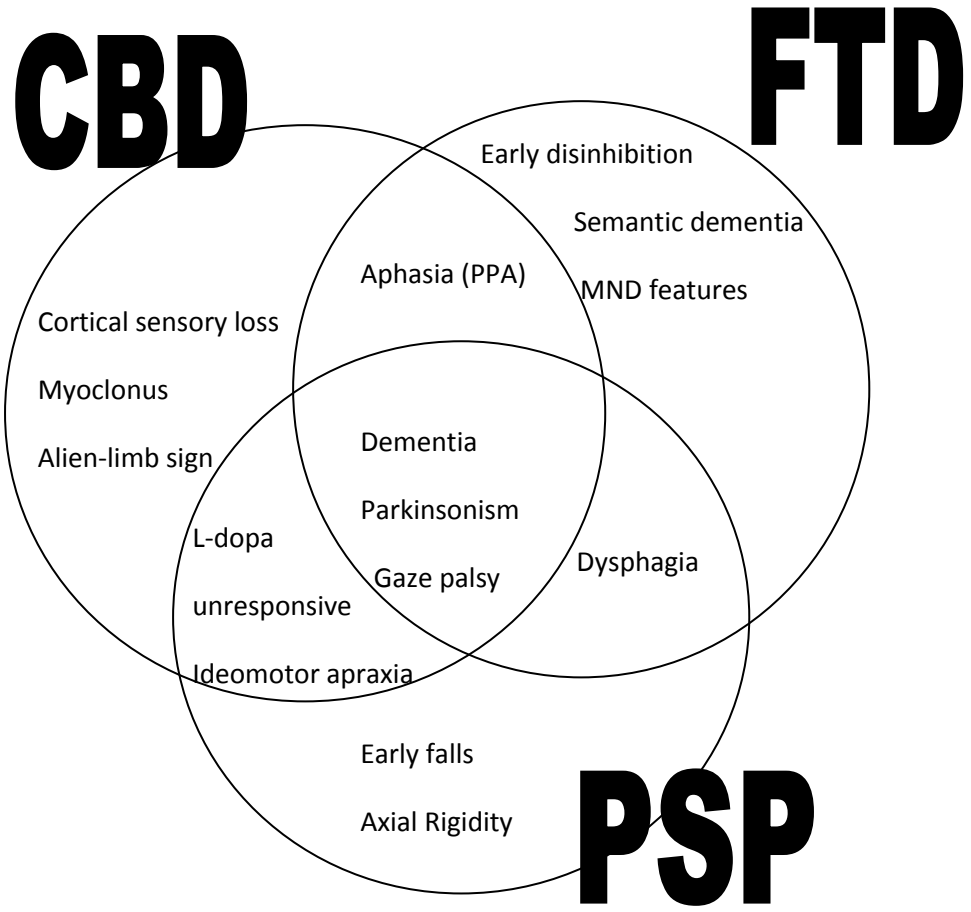
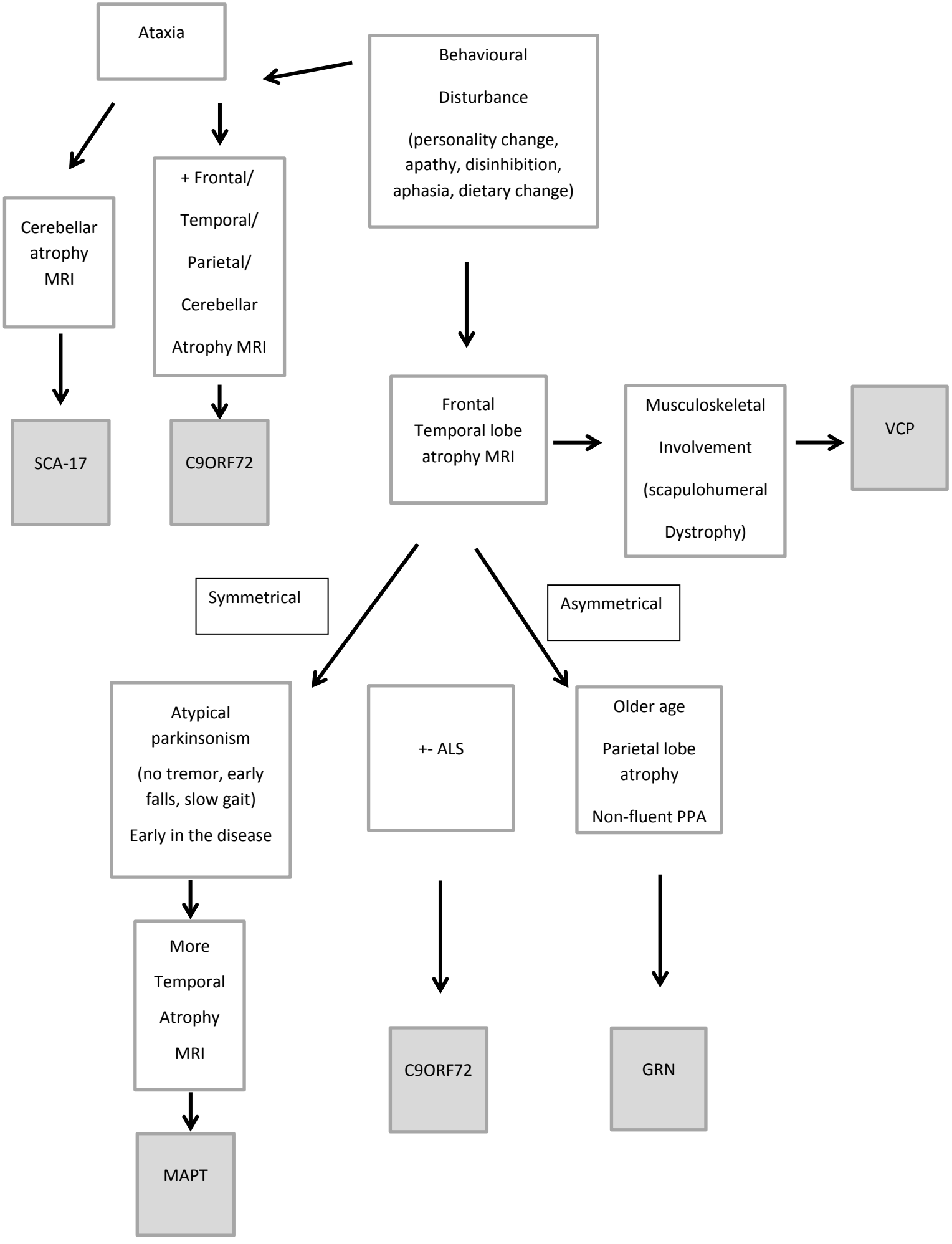


Figure 2: A diagnostic approach to frontotemporal dementia



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