

Overview of the non-Alzheimer Dementias

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Disclaimer

- Dr. Onyike is a principal investigator for the Baltimore site of a multicenter trial of memantine for treatment of FTD
- All references to prescription medicines pertain to “off-label” prescribing
- Many non-pharmacological interventions described here derive from adaptations or innovation
- No benefits in any form have been or will be received from a commercial party related directly or indirectly to the subject of this talk

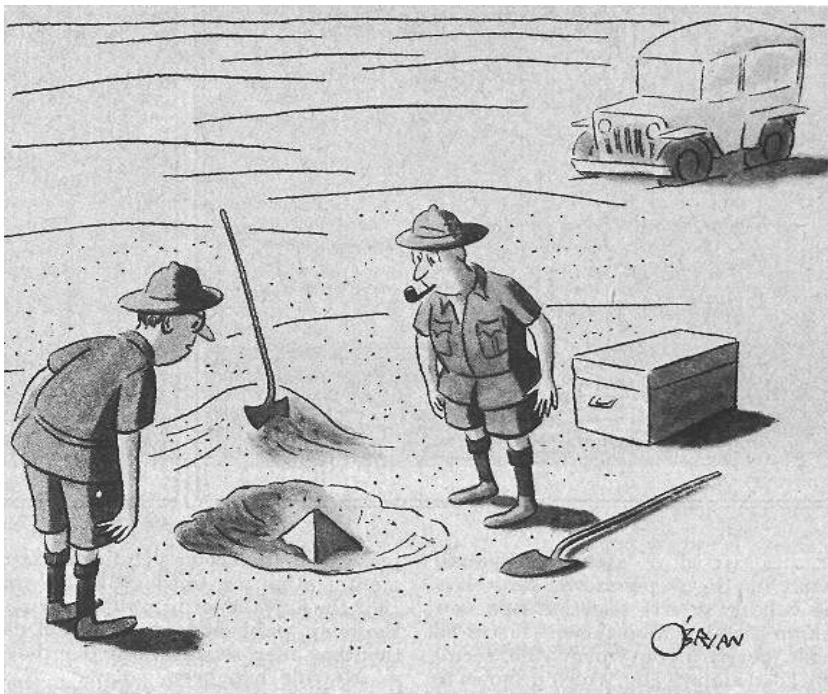
Vignette 1

- *A 55-year-old former technician developed difficulty finding words. Two years later he manifested dysfluency, repetition of remarks and questions, stereotypies (habitual use of meaningless phrases) and echolalia (reflexive repetition of another's speech). He developed poor reasoning and self-organization, and was unfeeling, intrusive, childlike and impulsive. Routines became rigid (e.g., insistence on exact TV shows), manners coarsened (e.g., eating out of serving bowls, jumping queues, walking from conversation) and restlessness was marked - each day he biked, swam many laps, ran 6.5 miles, and walked all day. During exam, he was pleasant and cooperative. At every opportunity he quizzed the examiner on trivial facts (such as asking for a listing of foreign capitals). Depression was not evident, and he did not have euphoria, psychosis, or paranoia. Speech was mildly nonfluent. Verbal fluency was impaired. Mini-mental state exam (MMSE) score was 29. Brain MRI showed marked right temporal atrophy.*

Vignette 2

- *A 61-year-old former negotiator developed reduced initiative and activity. Interest in favorite pastimes declined. After 18 months, he conversed less and lacked vitality. Retropulsion developed. MMSE score was 27. He had facial dyspraxias and slight rigidity of the right limbs. Brain MRI was normal. Brain PET showed hypometabolism in the right inferior frontal, parietal and anterior/inferior temporal lobes. One year later, memory was still intact, but speech was slower and less fluent and apraxias prevented driving, typing, or even stirring a pot. He tilted to the right when walking, had difficulty rising from a chair, often bumped into things, stumbled when walking and fell more often. He developed anxiety and he flailed arms and legs during sleep. MMSE was 30. Comprehension declined in the following year, speech distortions developed and coughing was frequent. Difficulty directing his gaze had developed, and limb apraxias and rigidity became predominantly right-sided. Jaw and deep tendon reflexes were pronounced. Gait was apractic. MMSE was 27.*

Features in non-Alzheimer dementias



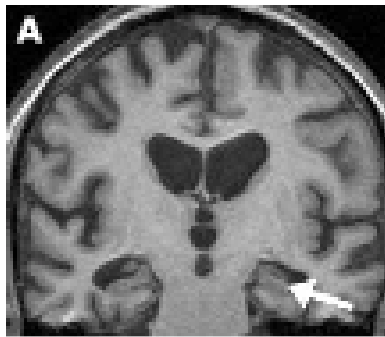
"This could be the discovery of the century. Depending, of course, on how far down it goes."

- ❑ Occurrence earlier in life – in the 5th and 6th decades
- ❑ Memory disturbance is NOT a prominent feature
- ❑ Predominance of disruption of executive & social cognition, speech/language and motor functions
- ❑ Brain imaging shows focal abnormality
- ❑ Low usefulness of the MMSE

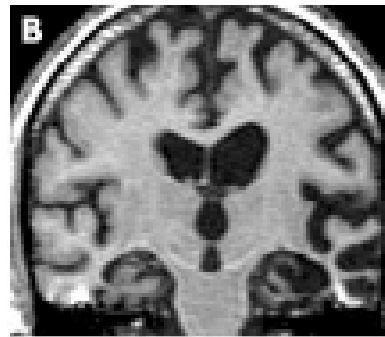
Phenotypes

- FTD (behavioral variant FTD): asocial, impulsive behavior
- Semantic dementia: loss of word and object knowledge, asocial behavior
- Progressive non-fluent aphasia: loss of fluency and grammar
- Corticobasal degeneration, CBD: Unilateral apraxia, parkinsonism, motor dyscontrol and dementia
- Progressive supranuclear palsy, PSP: vertical gaze palsy, parkinsonism, pseudobulbar palsy, retropulsion and falls, dementia
- Primary prosopagnosia with visual agnosia: loss of face and object knowledge

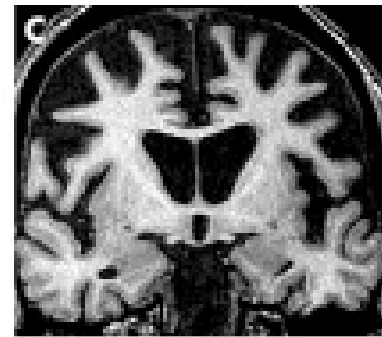
Brain imaging in the diagnosis of dementia



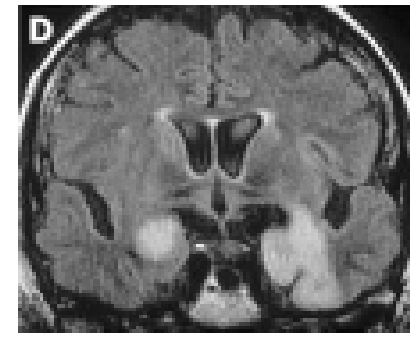
Alzheimer's disease



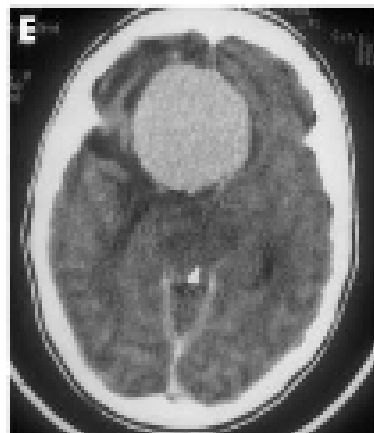
Semantic dementia



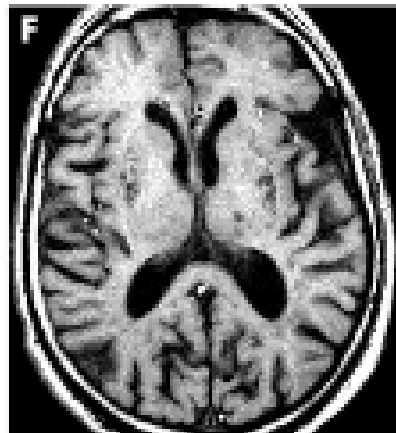
Frontal dementia



Limbic encephalitis



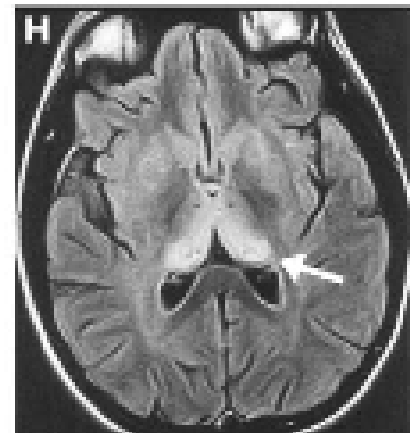
Tumour



Lacunar state



CADASIL

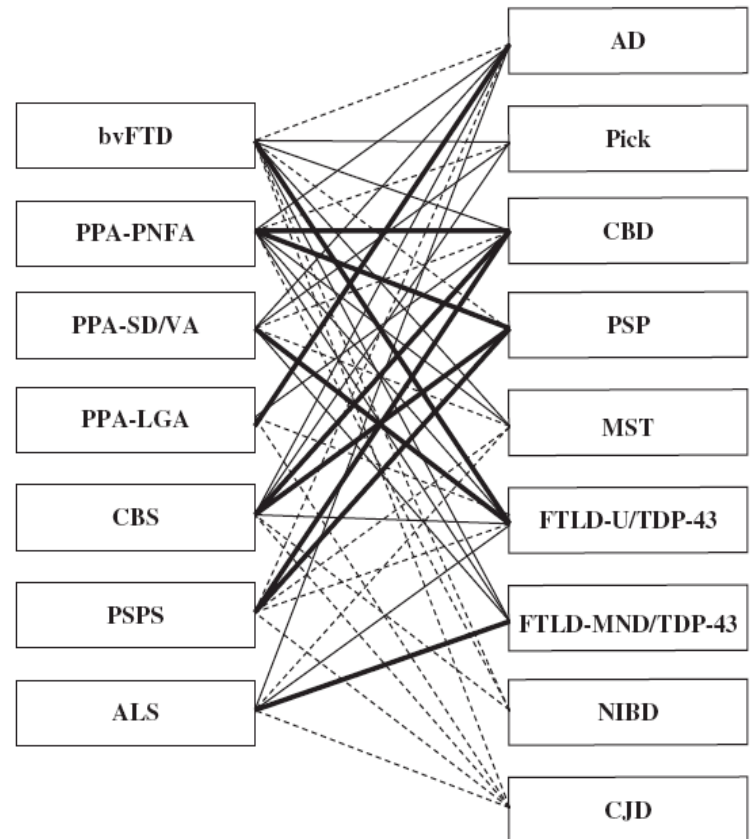


nvCID

Phenotypic heterogeneity

Boeve 2007

- Heterogeneity is marked in FTD
- Clinical and pathological phenotypes overlap
- Diagnosis is largely clinical
- Incorporation of genetic testing is beginning



Overlap with psychiatric phenotypes

Velakoulis et al., 2009

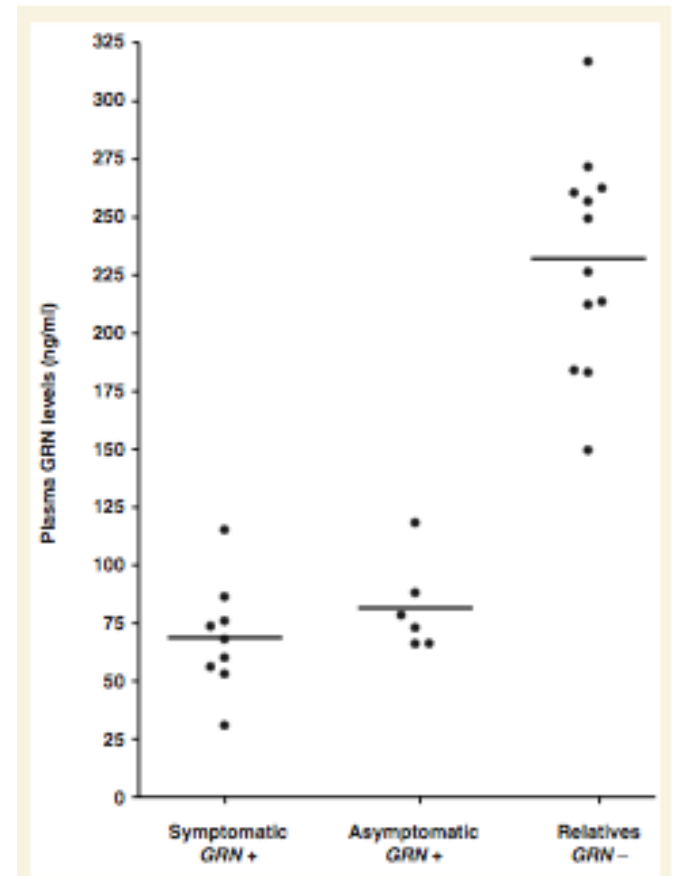
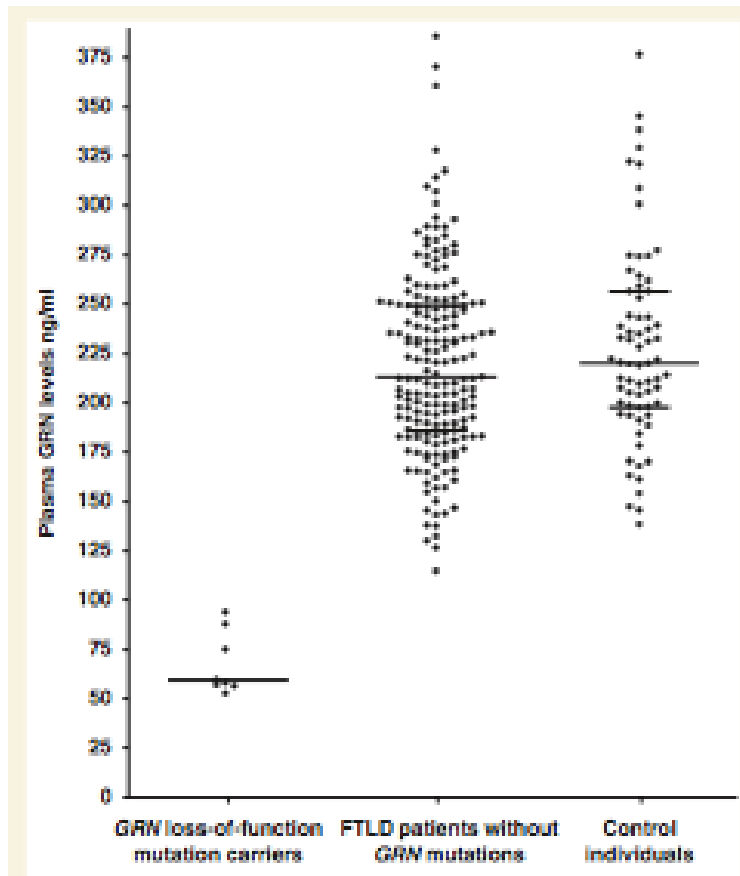
	Gender	Age, years			Clinical presentation	Tau	Ubiquitin	TDP-43	Diagnosis	Family history
		Onset	Presentation	Death						
Case 1	F	21	22	25	Depression, cognitive decline	+	-	Normal	FTDP-17	None
Case 2	M	28	33	37	Schizophrenia	-	+	+	FTD-MND	None
Case 3	M	NR	37	46	Apathy/disinhibition	-	-	NR	DLDH	NR
Case 4	M	34	39	41	Bipolar disorder	-	+	Normal	FTD-U	None
Case 5	M	35	39	43	Schizophrenia	-	+	+	FTD-MND	None
Case 6	M	37	40	44	Depression/apathy	-	+	+	FTD-U (progranulin mutation)	Presenile dementia maternal side
Case 7 ^a	M	38	43	45	Schizophrenia	-	+	NR	FTD-ID	FTD-MND
Case 8 ^b	M	43	46	49	Apathy	+	-	+	FTDP-17	FTDP-17
Case 9	M	43	49	61	Schizophrenia	-	+	+	FTD-ID	None
Case 10	F	NR	50	63	Cognitive decline	+	-	Normal	FTDP-17	Young-onset dementia in mother
Case 11	M	45	50	63	Cognitive decline, apathy	-	+	NR	FTD-U	MND in father
Case 12 ^c	M	NR	51	62	Cognitive decline	+	-	Normal	FTDP-17	FTDP-17
Case 13	F	50	53	64	Cognitive decline	-	+	NR	FTD-U	Senile dementia in mother
Case 14	F	49	55	66	Cognitive decline	-	+	+	FTD-ID	None
Case 15	M	56	57	59	Cognitive decline/PSP	+	-	Normal	PSP	Alzheimer's disease (mother)
Case 16	M	58	59	60	Disinhibition, cognitive decline	-	+	+	FTD-ID	None
Case 17 ^d	F	59	62	65	Cognitive decline	-	+	+	FTD-MND	None

Genetics for diagnosis

- Testing for hereditary and sporadic mutations:
 - MAPT for FTD-tau (Pick's, FTD-P, CBD, PSP)
 - PGRN for FTD-TDP43 (FTD-MND, semantic dementia)
 - FUS for FTD-U (FTD-MND, FTD-IF, BIBD)
 - Presenilin-1 (mutations manifest AD dementias that may fully mimic FTD)
 - CHMP2B
 - VCP for IBMPFD

Serum progranulin for FTD

Finch et al., 2009



Challenges in care for non-Alzheimer dementias

- Difficult/delayed diagnosis
- Limited professional knowledge
- Uncommon behavior problems
- Limited availability of treatment
- Limited appropriate supportive care structures
- Lack of natural peer groups
- Loss of employment
- Complex home environments
- Financial pressures

Pharmacotherapy in FTD

Agent	Target
Trazodone*	Irritability, disinhibition, insomnia
SSRI & SNRI*	Depression, irritability, disinhibition, impulsions, compulsions
Neuroleptics	Irritability, agitation, aggression
Benzodiazepines	Short-term treatment of agitation and aggression
Stimulants	Distractibility, restlessness, apathy, depression
Dopamine agonists	Apathy, inertia
Mirtazapine	Insomnia, restlessness, irritability
Amantadine	Inattention/distractibility, disorganization, perseverations
Anticonvulsants	Topiramate for gluttony? Others for irritability, aggression, impulsions
α 2-antagonists	Inattention/distractibility, disorganization, perseverations
AchEI	Not indicated

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