Adult Grand Rounds

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M. Schoenberg

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C. Evans

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The man who used to know everything

Grand Rounds - Adult
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- I have ***no relevant*** financial relationships to disclose:

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Demographics

- 47 year old, right handed, Filipino man
- Born in Germany, raised throughout the world (U.S. Military Family)
- 12 years of education; completed in English
  - Academic history largely known
- Married once, two children (ages 4 and 6)
- Employed full-time in shipping/receiving; worked the docks
  - Released from employment 4 weeks prior to present evaluation secondary to declining performance
  - On FMLA at time of eval

Referral Question

- Presented to outpatient neurology center, specializing in neurodegenerative disease
  - Primary complaints: short and long term memory loss
- Evaluated by cognitive disorders neurologist
  - Severe impairment noted on cognitive screening (MoCA = 7/30)
  - Neurological exam was unremarkable
- Patient was clinically referred for differential diagnosis and treatment planning
  - Question about need for permanent disability had been raised

Relevant History

- September 2016:
  - Patient has 2nd heart attack (first in 2004); multiple stents placed without complications
  - Was reportedly doing okay after hospitalization
- December 2016:
  - Patient's wife begins noticing that he is having difficulty completing routine tasks around the home (e.g., forgetting items while grocery shopping)
- July 2017:
  - Patient's memory declined markedly
    - Difficulty recalling names of family members (inc. children, wife)
    - Still working, but employer had to make changes to accommodate patient
    - Started becoming less engaged with family members
    - Had been fully independent in all basic and complex ADLs

Relevant History – Hospitalization

- July 2017
  - Emergently admitted to hospital by PCP
    - Hospital workup: noncontrast MRI, MRA, EEG
    - Only finding was a small posterior fossa cyst (18mm); all studies otherwise normal
  - Attending physician questioned whether Brilinta was the cause
    - Only treatment change was to replace with Brilinta with clopidogrel
    - Discharged home in stable condition, without supports

Relevant History

- July 2017 – March 2018:
  - Patient continued to decline cognitively
  - Lost his job as a laborer; on FLMA and determining the need for permanent disability
- At time of eval (per wife):
  - Starting to get "pieces" of his memory back
  - Not asking repetitive questions as often
  - Has been more outgoing, like his old self
  - Resumed speaking with cousins and other family members
  - Able to go to the store with a list and get all items

Presenting Complaints – March 2018

- Majority of his long term and autobiographical memory are gone
  - Unable to state his mother's name, where he was born and raised, the name of his last employer, the name of his children's school, where his wife works, or any recent president.
- Remembers daily schedule without error
  - Dropping his wife off at work
  - Taking his children to and from school
  - Does not get lost while driving
- Recognizes faces readily (though may not always remember the name)
- Significant problems with auditory comprehension
  - Often requires simplification and repetition to ensure he understands
  - No reports of expressive language difficulty

Presenting Complaints – March 2018

- Patient stated that he is "sad at myself" when asked about his mood
- Acknowledged getting easily frustrated and his wife noted that he has seemed a bit more moody lately, though this is improving.
- Problems with significant apathy; requires prompting to engage in most tasks, though there is no clear anhedonia.
- Suicidal ideation, delusions, and hallucinations were denied.
- Eating less and reports that food does not taste good
  - Lost a considerable amount of weight in the past year
  - No apparent cravings or changes in food preferences.
- Sleep problems denied
  - No reports of REM sleep behavior disorder

Additional History

- Past Medical History
  - 1st Heart attack (2004)
  - 2nd Heart attack with multiple coronary stents placed (2016)
    - No known complications
  - Hypertension
  - High cholesterol
  - Coronary artery disease
  - Obstructive sleep apnea (treated)
  - Diabetes mellitus (most recent A1c = 5.7)
- Past Psychiatric history: none
- Family History: late onset of unspecified dementia (paternal grandmother and 2 paternal uncles)

Current Medications

- Aspirin (low dose)
- Levocetirizine (5mg/day)
- Atorvastatin (20mg/day)
- Clopidogrel (75mg/day)
- Metformin (2000mg/day)
- Losartan (50mg/day)
- Fluticasone

Preliminary Hypotheses

- Anoxic injury (heart attack; surgical complication)
- Stroke
- Paraneoplastic syndrome
- Brain tumor
- Malingering
- Medication side effects
- Toxic exposure
- Prion disease

Test battery

- Boston Naming Test
- Delis-Kaplan Executive Functioning System
  - Color Word Interference
  - Trail Making
  - Verbal Fluency
- Hopkins Verbal Learning Test, Revised
- Brief Visuospatial Memory Test, Revised
- Wechsler Memory Scale, 4th Ed. – Logical Memory
- Judgment of Line Orientation
- Wechsler Adult Intelligence Scale, 4th Ed.
  - Block Design
  - Visual Puzzles
  - Coding
  - Digit Span
  - Similarities
- Test of Practical Judgment
- Wide Range Achievement Test, 4th Ed. – Reading
- Medical Symptom Validity Test
- Test of Memory Malingering
- Geriatric Depression Scale

Behavioral Observations – Interview

- Alert and oriented to person, day, and month
  - Able to identify the date and year with a logical cue
  - Unable to identify the city, state, or name of the clinic even with multiple choice cues
- Affect was very flat and restricted, but pleasant with examiner
- No apparent speech or language errors present
- Speech was soft and slow, but normal rhythm, tone, and prosody
- Expressive language was simple with very short utterances and use of repetitive stock phrases
  - (e.g., referring to his wife as "the love of my life" and "I used to know everything")
- Thinking was very concrete and literal
  - Only responded to direct questions and had significant difficulty answering
  - No indication of delusion or disorganization.

Behavioral Observations – Testing

- Easily confused with test instructions and required significant elaboration, simplification, demonstration, and repetition
- Worked slowly but consistently; no evidence of distractibility or disinhibition
- Appeared to stare blankly at test materials without responding but when prompted, he defensively noted that he was trying to work through the item
- Unable to comprehend hypothetical situations intended to elicit judgment and decision making (TOPJ), even with elaboration
- Unable to complete emotional symptom inventories due to comprehension problems and had difficulty recognizing letters on the WRAT-4 Reading subtest
- No difficulty with TMT
- Unable to name a single animal during verbal fluency (!)
- 2 of 60 items correctly on BNT (!!)

Results – Validity

- Behavioral Observations
  - Loss of autobiographical memory
  - Contrast between daily functioning and presenting complaints
  - BNT and animal naming scores
  - Trouble with letter sequencing but normal number-letter sequencing
- TOMM:
  - Trial 1 = 46
  - Trial 2 = 49
- MSVT:
  - Immediate Recall = 95
  - Delayed Recall = 95
  - Consistency = 90
  - Paired Associates = 0
  - Free Recall = 15
- Reliable Digit Span = 6

VALID OR INVALID?

Results

	Raw Score	Standard Score	Prev. Testing	%ile	Rating
WRAT-4 Reading	18	55	---	<1	Impaired
Wechsler Memory Scale, 4th Ed.		*(Scaled Score)*			
Logical Memory Immediate Recall	1	1	---	<1	Impaired
Logical Memory Delayed Recall	1	1	---	<1	Impaired
Logical Memory Recognition	18	---	---	3-9	Mildly Impaire
Hopkins Verbal Learning Test		*(T-Score)*			
Trial 1 / 2 / 3	(1/1/1)	(19/19/19)	---	---	---
Total Recall	3	19	---	<1	Impaired
Delayed Recall	0	19	---	<1	Impaired
Percent Retention	0	19	---	<1	Impaired
Rec. Discrimination (H / FA) (5/9)	-4	19	---	<1	Impaired
Brief Visuospatial Memory Test, Revised		*(T-Score)*			
Trial 1 / 2 / 3	(1/1/3)	(25/19/19)	---	---	---
Total Recall	5	19	---	<1	Impaired
Delayed Recall	1	19	---	<1	Impaired
Percent Retained	33	---	---	<1	Impaired
Discrimination Index (H / FA) (5/0)	5	---	---	11-16	Low Average

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Results

Attention / Working Memory / Processing Speed							
D-KEFS Trail Making Test							
Scanning	Errors:	0	35	5	---	5	Mild Imp.
Numbers	Errors:	0	50	6	---	9	Low Avg.
Letters	Errors:	0	59	3	---	1	Impaired
Speed	Errors:	0	34	10	---	50	Average
D-KEFS Color-Word Interference							
Color Naming	Errors:	5uc, 2sc	90	1	---	<1	Impaired
Word Reading	Errors:	0uc, 1sc	68	1	---	<1	Impaired
WAIS-IV Coding			44	6	---	9	Low Avg.
WAIS-IV Digit Span Total			15	4	---	2	Mild Imp.
Forward	LDSF:	4	6	5	---	5	Mild Imp.
Backward	LDSB:	3	5	6	---	9	Low Avg.
Sequencing	LDSS:	3	4	5	---	5	Mild Imp.

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Results

Language						
Boston Naming Test		2	T = 9	---	---	--
Visual Perception/Organization						
BVMT - Copy		10	---	---	---	WNL
Judgment of Line Orientation		23	---	---	---	--
WAIS-IV Block Design		24	6	---	9	Low Avg.
WAIS-IV Visual Puzzles		7	6	---	9	Low Avg.
Executive Functioning						
WAIS-IV Similarities		0	1	---	<1	Impaired
Delis-Kaplan Executive Functioning System			*(DKEFS)*	*(MOANS)*		
Phonemic Fluency (FAS)	(4/7/4)	15	3	-2.65	1	Impaired
Animals		0	---	-4.06	---	---
Category Fluency (Animals, Boys names)		5	1	---	<1	Impaired
Category Switching		0	1	---	<1	Impaired
CW Inhibition	Errors: 2uc, 0sc	180	1	---	<1	Impaired
CW Switching	Errors: 1uc, 0sc	177	1	---	<1	Impaired
Trails Switching	Errors: 0	98	8	---	25	Average

VALID OR INVALID?

CLINICAL IMPRESSIONS

Confirmatory bias

- The tendency to search for, interpret, favor, and recall information in a way that confirms one's preexisting beliefs or hypotheses (Plous, 1999)
  - Selective gathering of supporting info and neglect of contradictory info
  - Particularly prevalent in forensic settings (Satya-Murti and Lockhart, 2015)
- Avoid by intentionally seeking out disconfirming evidence
  - E.g., are there other reasons why this person might have done so badly?
- Multidisciplinary clinics may be less vulnerable to these biases because of the wealth of additional information available
  - Updated neuroimaging drastically changed clinical impressions

Evidence of malingering

Supporting

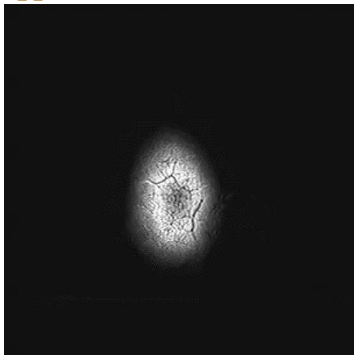
- Very young for almost all neurodegenerative disease
- Loss of autobiographical information unusual, even for severe dementia
- Level of cognitive impairment highly discordant with functioning
- Normal neurological exam
- Historical imaging reported normal
- Disability claim pending

Disconfirming

- Passed all validity indices
  - ➢ Could he have been coached?
- Expressive language errors (i.e., repetitive stock phrases)
- Evidence of poor comprehension

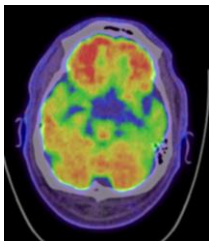
Disconfirming Evidence – Brain MRI

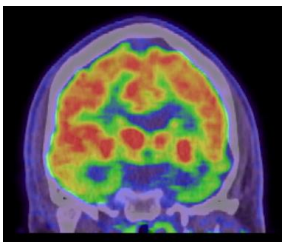
- No evidence of an acute intracranial process or intracranial mass.
- Moderate generalized volume loss by visual inspection.
- Hippocampal volumes at the 1st percentile when compared to age matched normal controls by quantitative analysis
  - Severe hippocampal formation volume loss by visual inspection.
- Minimal white matter disease which is nonspecific but likely reflective of chronic microvascular ischemia.

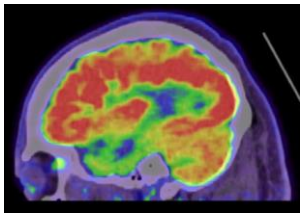


FDG-PET

- Diffuse cortical hypometabolism, more pronounced in association cortex in bilateral temporal, left parietal, occipital and frontal regions
- Distribution pattern suggests neurodegenerative disorders with differentials including diffuse Lewy-body dementia
- Other less likely differentials include temporal dominant atypical Alzheimer's dementia, frontotemporal dementia







CLINICAL IMPRESSIONS

Clinical Diagnosis – Semantic dementia

I. Clinical diagnosis of semantic variant PPA
Both of the following core features must be present:
1. Impaired confrontation naming
2. Impaired single-word comprehension
At least 3 of the following other diagnostic features must be present:
1. Impaired object knowledge, particularly for low-frequency or low-familiarity items
2. Surface dyslexia or dysgraphia
3. Spared repetition
4. Spared speech production (grammar and motor speech)
II. Imaging-supported semantic variant PPA diagnosis
Both of the following criteria must be present:
1. Clinical diagnosis of semantic variant PPA
2. Imaging must show one or more of the following results:
a. Predominant anterior temporal lobe atrophy
b. Predominant anterior temporal hypoperfusion or hypometabolism on SPECT or PET

Gorno-Tempini, et al. (2011)

- Variant of frontotemporal dementia (FTD)
- Further subtyped as a primary progressive aphasia (PPA)
  - Semantic dementia is primarily characterized by loss of semantic knowledge
  - Presents as anomia and single-word comprehension deficits
  - With progression, stock phrases become common
- Brain atrophy typically greater on the left
- Caused by accumulation of TDP-43
- Typical age of onset: 50s – 60s
- Limited inheritance

Conclusions

- Confirmatory bias is a common source of error in clinical decision making
  - Must remain vigilant for it and actively seek disconfirming evidence
- Veracity of PVTs:
  - Patient with severe, nearly global impairment
    - Still able to perform above criterion on TOMM and MSVT
  - Patient with severe loss of semantic knowledge
    - Still able to perform above criterion on TOMM and MSVT!
  - Hippocampus almost completely absent (quantified at 1st percentile)
    - Still able to perform above criterion on TOMM and MSVT!!

History of Nonverbal Learning Disability (NLD)

- Study of LD began around 1890 (Spreen, 2011)
- Initially focused on ability to read and write (Orton, 1937)
- "Nonverbal Disorders of Learning" & "Nonverbal Learning Disability" (Johnson & Myklebust, 1967; Myklebust, 1975)
  - Selective deficits in: perception, processing of gestures, motor learning, body image, spatial orientation, and left-right orientation
- Furthered by the work of Byron Rourke (1989 & 1995)
  - Visual-spatial learning
  - Tactile and motor skills
  - Mathematics

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Controversy

- Definition of a learning disability
- Variable diagnostic criteria creating tautological problems
- Methodological issues in the literature

(Fine et al., 2013 & Spreen, 2011)

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Proposed Diagnostic Criteria for NLD

- *Criterion A.* A persistent deficit in one or more measures of nonverbal intelligence or reasoning in the presence of an average or above-average verbal intelligence
- *Criterion B.* Substantial weaknesses, currently or emerging from the child's history, in processing visuospatial information, as manifested by at least two of the following weaknesses
  1. Difficulties in perceiving organized forms
  2. Difficulties in reproducing simple drawings by copy or memory
  3. Difficulties in temporarily remembering and manipulating visuospatial information

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Cornoldi, C., Mammarella, I. C., & Fine, J. G., 2016

Proposed Diagnostic Criteria for NLD, Cont.

- *Criterion C.* Presence of clinical and/or psychometric indexes of weaknesses in at least one of the following areas, currently or by history
  1. Fine-motor impairments including praxis and/or output
  2. Poor academic achievement in activities involving visuospatial skills, mathematics, or other, in the presence of an average or above-average performance in reading decoding tasks
  3. Difficulties in social interactions

Cornoldi, C., Mammarella, I. C., & Fine, J. G. (2016)

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Proposed Diagnostic Criteria for NLD, Cont.

- *Criterion D.* Several symptoms were present before age 7, although they could not have become fully manifest until academic demands exceeded the children's capacities, or were masked by good verbal strategies
- *Criterion E.* There is clear evidence that the symptoms interfere with, or reduce the quality of, academic, occupational, or social functioning
- *Criterion F.* These disorders are not better explained by the presence:
  - ASD
  - DCD
  - ID
  - Neurological and/or genetic conditions

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Cornoldi, C., Mammarella, I. C., & Fine, J. G. (2016)

Case Presentation

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Case Presentation

- Demographic Data
  - 25 year-old, single, non-Hispanic White female completing her 16th year of education; majoring in English
  - English is her only language
- Referral
  - Differential diagnosis of ADHD and LD
  - Accommodations

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Pertinent Psychosocial / Educational History

- Normal Pregnancy, met all developmental milestones on time.
- "Average" grades throughout elementary school (public school)
  - Reported multiple reading evaluations
  - Speech therapy in 2nd, 3rd, & 4th grades
- Home schooled for middle school and high school
- Did not take test for high school diploma "because of test anxiety"
- Passed GED exam on the fourth attempt
- Received accommodation in college
  - Extended time for writing
- Reported that she needed additional accommodations for math and reading

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Pertinent Medical History

- Headaches
  - Migraines: 3 per year
  - Tension: 4 per month
- "Hypermobility Syndrome" in hands
- Sleep
  - Sleep apnea (on CPAP)
- Unremarkable neurological history

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Psychosocial History

- Mood: "More angry than I should be and extremely stressed out."
- Lifelong anxiety
  - Hair pulling
  - Hitting
- Depression and passive SI beginning at 15 years old
- Currently participating in psychotherapy – "Helpful"

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Collateral Report (Mother)

- Spoke in full sentences at 18 months and was able to read before starting the first grade
- ADHD Symptoms (since toddlerhood)
  - Missing details/producing inaccurate work
  - Easily distracted
  - Not sustaining attention
  - Starting but not completing work
  - Maintaining a messy environment
  - Losing personal belongings
- Deficits negatively impacted her academic performance, social interaction, and relationships with teachers
- "Good grades" precluded her from being tested for ADHD and LD
- Lifelong Anxiety

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hief Complaints

- Attention Deficits
  - Missing details/producing inaccurate work
  - Difficulty sustaining attention
  - Not listening when spoken to
  - Starting but not finishing work
  - Maintaining a messy/disorganized environment
  - Avoiding tasks that require sustained mental effort
  - Losing personal belongings frequently
  - Becoming easily distracted
- Hyperactivity
  - Fidgeting/squirming
  - Leaving her seat and running at in appropriate times when younger
  - Difficulty engaging in leisurely activities
  - Feeling driven by a motor
  - Talking excessively
  - Interrupting others
  - Difficulty waiting her turn
- Mathematics
  - Transposing numbers
  - Mixing up math signs
  - No improvement following tutoring

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Test Results

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Behavioral Observations

- Braces on her hands bilaterally
- Appropriate eye contact
- Adequate interpersonal skills
- Difficulty sitting still
- Easily distracted
- Tangential

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Performance Validity

WMT	%
IR	92.5
DR	97.5
CNS	90

	Raw
ACS Word Choice	50

RDS	Raw	RDS	Overall Clinical Sample
Forward	5	10	≤75%
Backward	5		

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Intellectual Functioning

WAIS-IV	SS	
VCI	150	
PRI	77	
WMI	92	
PSI	76	
FSIQ	102	
	Raw	SS
Similarities	36	19
Vocabulary	55	19
Block Design	24	6
Matrix Reasoning	12	6
Digit Span	29	9
Arithmetic	11	8
Symbol Search	23	6
Coding	44	5

Comparison to the Overall Normative Sample		
	Raw	Cumulative %age
VCI-PRI	73	<0.2
VCI-WMI	58	<0.1
VCI-PSI	74	1
PRI-WMI	-15	13.1
PRI-PSI	1	47
WMI-PSI	16	14.9

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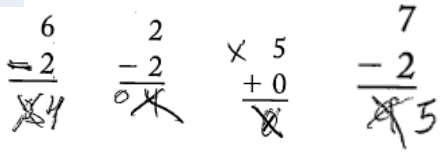
Achievement

WJ-IV Achievement	SS
Reading	110
Broad Reading	101
Basic Reading Skills	115
Reading Fluency	98
	SS
Letter-Word Identification	105
Passage Comprehension	114
Word Attack	127
Oral Reading	111
Sentence Reading Fluency	91

WJ-IV Achievement	SS
Mathematics	94
Broad Mathematics	84
Math Calculation Skills	75
	SS
Applied Problems	104
Calculation	86
Math Facts Fluency	70



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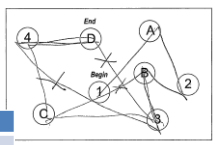
Attention, Speed, & Executive Functioning

	Raw	T
BTA Numbers	5	28
BTA Letters	6	33
BTA Total	11	28
Salthouse PCT LC	20	21
Salthouse PCT PC	27	24
CPT-3	T	
Omissions	49	
Commissions	63	
Hit RT	53	
Perseveration	48	

Sample



Stroop (Golden)	Raw	T
Word	77	28
Color	58	31
Color-Word	32	35
Interference	-1	49
TMT	Raw	T†
Part A	29	40
Part B	55	45
WCST-128	Raw	T
Total Categories	6	>16%ile
Perseverative Errors	12	48
Total Errors	21	51
FTMS	1	>16%ile
Trials to First Category	20	2-5%ile

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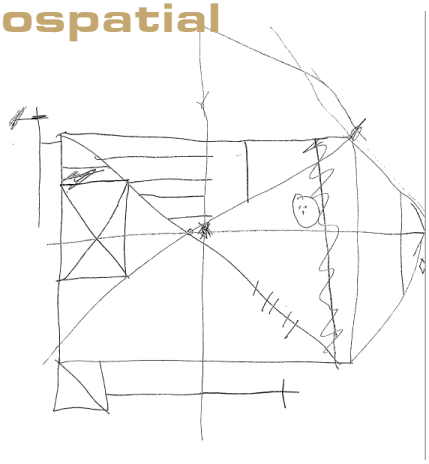
Visuospatial

Visuospatial	Raw	%ile
RCFT Copy Trial	29	<1



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CVLT-II	Raw	T
Trial 1	9	60
Trial 2	12	55
Trial 3	16	70
Trial 4	15	60
Trial 5	15	55
Total	67	65
Trial B	7	50
SDFR	15	60
SDCR	14	55
LDFR	16	65
LDCR	16	50
Intrusions	1	50
Repetitions	3	45
Rec. Hits	16	50
Rec. FP	0	45

WMS-R Logical Mem	Raw	T†
Immediate	41	69
Delayed	36	65

BVMT-R	Raw	T†
Total Recall	23	37
Delayed Recall	10	44
% Retention	100	52
Recog Discrimination	6	51

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Motor

Language	Raw	T†
CIFA Letter Fluency	37	60
CIFA Category Fluency	43	45

Motor	Raw	T‡
GPB Dominant	81	27
GPB Non-Dominant	100	26

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Self-Report: ADHD & Mood

	Raw	Descriptor
PHQ-9	14	Moderate
GAD-7	15	Severe
Epworth	16	Elevated
PSQI	11	Elevated

CAARS-S:L	Raw	T
Inattention/Memory	33	85
Hyperactivity/Restlessness	33	77
Impulsivity/Lability	23	69
Self-Concept	14	66
DSM-Inattentive Type	25	89
DSM – Hyperactive/Impulsive Type	22	79
DSM ADHD Total	47	90
ADHD Index	27	77
Inconsistency	6	--
CII	25	--

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Differential Diagnosis: ASD

- Absence of restrictive/repetitive patterns of behavior, interests, or activities
- More severe in ASD
  - Sameness/inflexible adherence to routines
  - Reactivity to sensory input
  - Pragmatic difficulties
    - Unusual prosody
    - Verbose speech
    - Difficulties interpreting jokes / figurative language
    - Lack of response to nonverbal social cues
- Difficulties with visuospatial reasoning not consistent in children with ASD

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Semrud-Clickeman et al., 2010

Differential Diagnosis: SLD

- Considerable overlap with mathematics LD
- Geary's (2004) 3-subtypes of mathematics LD
  - Procedural } More likely to be represented by pure mathematics LD
  - Semantic }
  - Visuospatial } More likely to be represented in NLD

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Mazzocco & Myers, 2003

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Differential Diagnosis: ADHD

- Similarities:
  - Difficulties in organizing tasks/activities
  - Visual sustained attention tasks
- Differences
  - NLD does well on verbal sustained attention tasks
  - Visuospatial < Verbal intelligence not documented within ADHD

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Semrud-Clickeman et al., 2010

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- *Criterion A.* A persistent deficit in one or more measures of nonverbal intelligence or reasoning in the presence of an average or above-average verbal intelligence
- *Criterion B.* Substantial weaknesses, currently or emerging from the child's history, in processing visuospatial information, as manifested by at least two of the following weaknesses
  1. Difficulties in perceiving organized forms
  2. Difficulties in reproducing simple drawings by copy or memory
  3. Difficulties in temporarily remembering and manipulating visuospatial information
- *Criterion C.* Presence of clinical and/or psychometric indexes of weaknesses in at least one of the following areas, currently or by history
  1. Fine-motor impairments including praxis and/or output
  2. Poor academic achievement in activities involving visuospatial skills, mathematics, or other, in the presence of an average or above-average performance in reading decoding tasks
  3. Difficulties in social interactions
- *Criterion D.* Several symptoms were present before age 7, although they could not have become fully manifest until academic demands exceeded the children's capacities, or were masked by good verbal strategies
- *Criterion E.* There is clear evidence that the symptoms interfere with, or reduce the quality of, academic, occupational, or social functioning
- *Criterion F.* These disorders are not better explained by the presence:
  - ASD
  - DCD
  - ID
  - Neurological and/or genetic conditions

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Treatment/Recommendations

- Psychiatric/social supports
  - Suicide safety plan
  - Medication management for mood
  - Behavioral activation
  - Improved sleep quality through use of sleep hygiene

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Treatment/Recommendations

- OT evaluation: fine motor dexterity and adaptation to visuospatial/perceptual challenges in day to day life
- Supports in day to day life for NLD, as it affects inattention:
  - Maintain an organizer with a schedule of daily events and reminders for assignments
  - Limit the number of distractions present when working
  - Budget extra time to complete tests and work knowing that you may become distracted
- Academic accommodations
  - Limit courses heavy in mathematic content
  - Participate in class discussions as much as possible to enhance concentration
  - Study with others to reinforce your understanding of the material
  - Always "over-learn" the material
  - Apply the concepts to a “real-life” scenario
  - Pace completion of mathematics homework
  - Do not move onto more complex math tasks until you have demonstrated mastery over foundational math concepts

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Questions…

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A Case of Progressive Dementia associated with Autoimmune Encephalitis

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17 October 2018

Purpose and Outline

Purpose: To present a case of progressive dementia associated with autoimmune encephalitis with N-type voltage gated calcium channel autoantibodies (VGCC abs)

The views expressed herein are those of the author and do not reflect the official policy or position of Brooke Army Medical Center, the U.S. Army Medical Department, the U.S. Army Office of the Surgeon General, the Department of the Army, the Department of the Air Force and Department of Defense or the U.S. Government.

Autoimmune Encephalitis

- Onset acute or subacute; typically over days or weeks
- Symptoms may include mood or behavioral changes, short-term memory problems, cognitive dysfunction, psychotic symptoms and possible seizures, sometimes catatonic state
- In about 50% of cases MRI normal
- EEG often abnormal for non-specific slow & disorganized brain wave activity
- Best known types are those with antibodies to NMDAR (Anti-N-Methyl-D-Aspartate Receptor) and VGKC (Voltage-gated potassium channel);
- Limbic encephalitis typically affects mesial temporal lobes (hippocampus) and orbitofrontal cortex but also the cerebellum

Tuzun & Dalmau 2007
Loughan et al. 2016

Autoimmune Encephalitis

- Treatment typically consists of steroids, IVIG, plasma exchange
- With early detection, more than 75% of patients with this type of encephalitis recover completely or have only mild neurological sequelae
- Neuropsychological deficits may be more lasting and can include persistent deficits in attention, working memory, episodic memory, and executive functions
- Patients who received immunotherapy during the initial onset had a better cognitive outcome than those who received immunotherapy later

Finke et al. 2012
Loughan et al. 2016

VGCC

- The VGCC's (voltage-gated calcium channels) are found in several cells, to include smooth and skeletal muscle fibers, endocrine cells, and neurons.
- VGCC's are located on the presynaptic membrane of the axon terminal, open by action potential and lead to the entry of calcium ions into the axon terminals
- Calcium influx results in movement of acetylcholine vesicles towards the presynaptic membrane and acetylcholine is released into the synaptic cleft.
- VGCC abs are divided into 5 types: L, P/Q, N, R, and T
- VGCC P/Q type and N type often associated with Lambert-Eaton Myasthenia Syndrome (LEMS) and lung cancer
- Presence of VGCC abs has been associated with both paraneoplastic and nonparaneoplastic cerebellar degeneration
- Bekircan-Kurt et al. 2015

Bekircan-Kurt et al. 2015

- Mayo 2016 study examined a group of 236 patients with VGCC-P/Q type or VGCC-N type
- Autoimmune neurological diagnoses included encephalopathy, ataxia, myelopathy, neuropathy, neuromuscular junction disorder, and myopathy; LEMS mostly diagnosed separately
- Frequencies of diagnoses higher for those with high titer vs. low or medium expressed as nanomoles per liter of serum
- High=1.00 nmol/L or greater N=7
- Medium=0.10-0.99 nmol/L N=79
- Low=0.04-0.10 nmol/L N=150
- Overall positive predictive value was low at only 22%
- Pts with low values had autoimmune neurological diagnoses in 19%, about 20% normal, but 60% another cause, often neurodegeneratve or records had insufficient data

Zalewski et al. 2016

Conditions Associated with VGCC abs

- Median age of neurological symptom onset 57 years
- 52% of seropositive patients were women
- Cognitive disorders occurred in 41/236 (17%) and included degenerative dementia, autoimmune encephalopathy, mild cognitive impairment, and cognitive disorder NOS
- 29/41 cases of cognitive disorder were seen in low titer patients
- Seizures were seen in 10/236 (4%), 7 in low titer patients
- Cerebellar ataxia in 9/236 (3.8%), 5 in low titer patients
- Headache disorders in 9/236 (3.8%)
- 30% of patients had co-existing neural autoantibodies
- CSF abnormal in 81%; elevated protein in 55 (23%), leukocytosis in 13 (5%)
- Authors recommend that seropositive results be interpreted in the clinical context of the individual patient Zalewski et al. 2016

VGCC ab Encephalitis

- Auto-antibodies against P/Q- and N-type voltage dependent calcium channels mimicking frontotemporal dementia
- 54 year old man presented with frontal disinhibition and cognitive decline over days to weeks; had a history of rheumatoid arthritis and thyroid eye disease
- MRI showed atrophy greater than would be expected for age; FDG-PET consistent with FTD
- Symptoms initially treated with medication but symptoms worsened and paraneoplastic panel obtained due to patient's history of autoimmune conditions
- Elevated antibodies to VGCC abs +0.24 (seropositive medium)
- Patient underwent 5 therapeutic plasma exchange sessions; notable improvement starting with third session

Younes et al. 2018

Encephalopathies & Dementias

- Autoimmune dementia and encephalopathies are complex disorders that can cause immune-mediated cognitive deficits and have confusing nomenclature
- Presentation varies from acute limbic encephalitis to subacute or chronic disorders of cognition mimicking neurodegenerative dementia
- May occur as a paraneoplastic phenomenon or an idiopathic autoimmune phenomenon.
- Important to evaluate for cancer
- The diagnosis of an autoimmune dementia requires the detection of objective improvements in cognitive decline after a course of immunotherapy

McKeon et al. 2010; McKeon 2016; Flanagan et al. 2016

Patient Background Information

- 54 yr old right-handed SM (Service Member) born and raised in Nigeria
- Grew up speaking both English and his native language
- Completed school through university in Nigeria, Master's Degree in Leadership Management through Liberty University while on active duty
- Achieved the rank of MSG (Master Sergeant, E-8), Military Occupational Specialty of 36B, Financial Management Technician
- 19 years time in service
- Married for 17 years, 5 children
- One deployment to Iraq, November 2005-November 2006; history of fall from helicopter 2005, blast exposure 2006 with no noted residual sequelae.
- Wife noted symptoms of PTSD upon SM's return from deployment

History of the Presenting Problem

- SM and wife abducted and held for 5 days while on a trip to visit family in Nigeria in December 2015
- SM reportedly beaten to include several blows to the head
- Diagnosed with Major Depressive Disorder in February 2016
- Very prominent psychomotor slowing, flat affect, looking at the floor and having difficulty making eye contact
- TBI Team noted mild confusion, poor attention/concentration, word-finding problems, difficulty getting to work on time, frequent HA's, occasionally hearing voices
- Commander concerned about "very slow to respond"
- Brief NP testing indicated general cognitive performance in the extremely low range of functioning
- Examiner concluded results were not indicative of SM's true neuropsychological status, multiple failures on PVT's

History of the Presenting Problem

- Neurology exam in May 2016 found incongruous R superior quadrantanopia
- MRI June 2016 scattered focal areas of R greater than L bilateral volume loss in the cerebellar hemispheres
- Also very minimal smooth diffuse pachymeningeal enhancement, more prominent in the anterior temporal lobes and overlying parietal convexities, could be wnl but radiologist suggested correlation with signs and symptoms of infectious etiology
- SM sent for inpatient treatment for PTSD and MDD in San Antonio
- Referred for NP testing by psychiatrist, degree of cognitive impairment seemed out of proportion for even severe PTSD and MDD

Past Medical & Symptom History

- AHLTA Electronic Medical Record (EMR)
- Collateral Interview with wife
- Wife noted problems with memory beginning in 2010, forgot children's birthdates for paperwork, called home to ask
- History of HA dating to 2010, diagnosed as migraine HA in March 2012 after a HA that lasted 2-3 days
- MRI in 2010 a small nonenhancing area of abnormal signal in the posterior medial right cerebellar hemisphere thought to suggest infarction at that time
- Additional medical problems in 2010 included chronic leukopenia, hx of pulmonary embolism, hx deep vein thrombosis x2, erectile dysfunction (autonomic? High percent in LEMS) and chronic back pain

Past Medical & Symptom History

- 2012 Memory deficits brought to the SM's attention by co-workers
- November 2012 Neurology exam: deficits in recall, multi-step commands, and visuospatial testing; twice incorrectly gave the year as 2011
- NP evaluation ordered but was not completed at that time
- MRI 2012 reported mixed porencephaly and encephalomalacia involving the right cerebellar hemisphere
- Noted in 2012 several month history of anxiety, depression, insomnia
- SM diagnosed with PTSD in 2014
- Per wife's report, SM had experienced auditory hallucinations for several years, prior to abduction, could not be attributed to severe PTSD

Presentation & NP Testing

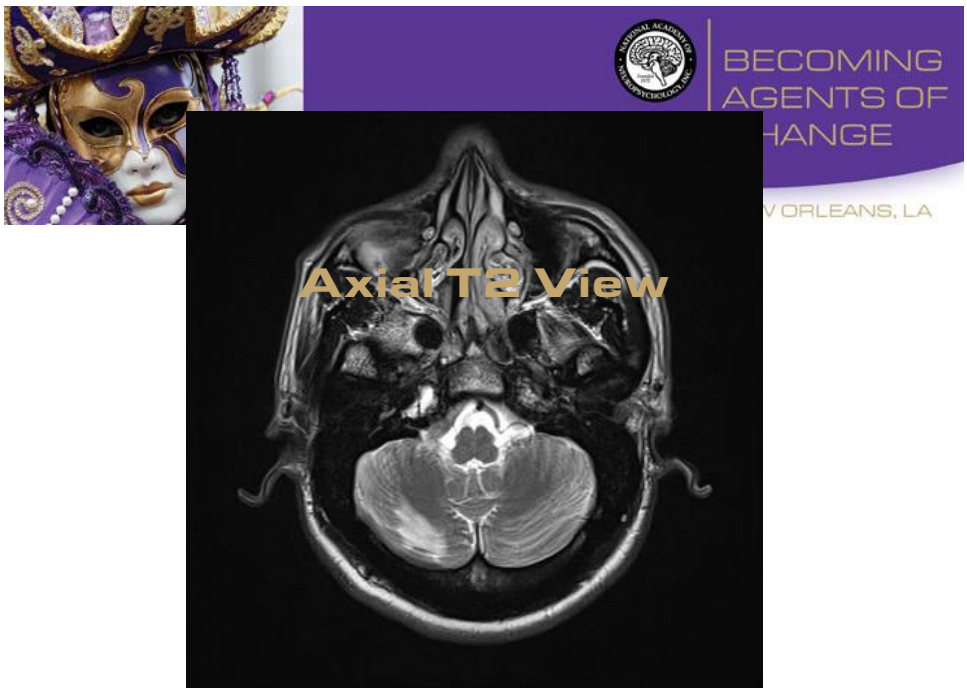
- Seen for NP testing August 2016
- Upon presentation to this provider the SM demonstrated very prominent psychomotor slowing, flat affect with little eye contact, speech was very sparse, mild occasional stuttering noted, SM was able to communicate that he was having difficulty with word-finding
- Neurocognitive functioning severely and almost globally impaired
- FSIQ=50
- NP attempted Category Test, 14 minutes to complete first two categories, D/C before Category III
- NP administered WCST, 55 minutes to administer, strongly perseverated to Form for about half of the test, then more disorganized, might get 3-5 correct but 4 FMS
- Trails B allowed to finish, 8+ minutes

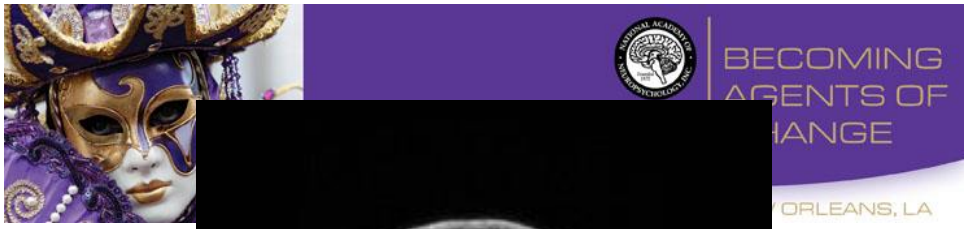
Presentation & NP Testing

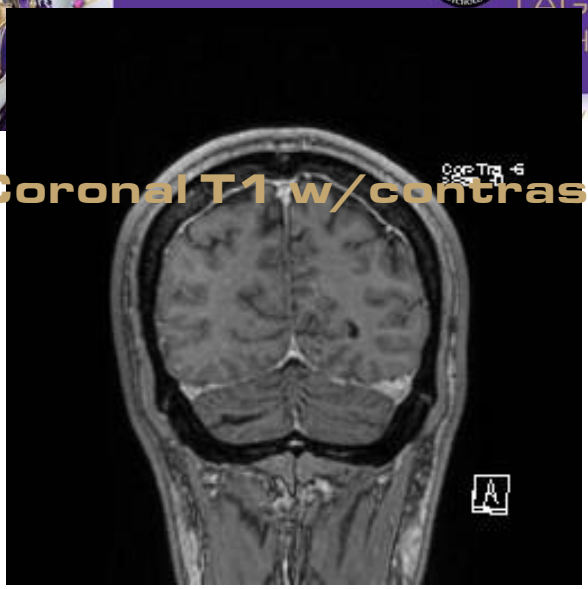
- CVLT-2 Moderate to severe impairment but able to give main points of the 2 LM passages and at delayed recall as well
- Visual Reproduction recalled a few bits of information and retained about half of those at 30 minutes
- Surprisingly copy of ROCF was accurate and well-organized, lost organization at immediate and delayed recall
- Performance in severely impaired range bilaterally on Finger Tapping, consistent with very slowed presentation
- Failed all PVT's
- SM appeared able to read and respond to BDI and BAI, reported clinically significant levels of depression and anxiety but no SI
- Wife reported declining levels of cognitive function since 2010, at time of evaluation unable to wash dishes correctly; ADL's intact but needed reminding; IADL's very impaired; got lost if not accompanied

Recommendations & Followup

- NP diagnosis of Major Neurocognitive Disorder (dementia)
- Recommended further evaluation for etiology of dementia, to include any possible reversible causes, specifically requested Neurology rule out limbic encephalitis
- Referred to Neuro-opthalmology due to previous finding of visual field defects
- EEG September 2017 Clinical impression: voltage of the electrocerebral activity very low, including the posterior dominant rhythm, but essentially normal
- Neuro-opthalmology found bilateral superior visual field defects, but again repeat MRI did not find correlated lesions for visual field defects
- MRI findings January 2017 read as stable R posterior inferior cerebellar encephalomalacia compared to June 2016 MRI







Neurology

- Neurologist thought findings suggestive of autoimmune encephalitis: past finding of protein in CSF 50% higher than normal; diffuse pachymeningeal enhancement; chronic HA's 3-4 times per week
- FDG PET found no evidence for FTD
- Genetic testing for genetic variants associated with FTD and ALS negative
- Paraneoplastic panel positive for N-type calcium channel antibodies
- Low clinical range 0.04-0.09 nmol/L, pt's results 0.07
- Neurologist felt nonparaneoplastic more likely due to long time course of decline
- Thus far continued evaluation for cancer to include full body PET negative, but some suspicious prostate findings
- Inpatient treatment with IVIG for 4 days, followed by treatment with monthly IVIG has produced functional improvement, thus far no repeat NP testing

Summary

- This case study illustrates the course of a progressive dementia over about a 5 year period of time, seropositive for VGCC N-type antibody
- Some recovery with treatment; potential for recovery unclear
- Consideration of an autoimmune encephalitis as one of the possible reversible causes for progressive dementia may result in earlier diagnosis, earlier treatment, better recovery

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