Aggressive evaluation, management and monitoring of MCI/dementia syndromes

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Of approximately 1770 patients over the age of 50 years old referred to the Falls Memory Center from 2007-present, approximately 1020 or 58% have MCI or neurodegenerative disorders. The majority of these patients present with amnesic MCI (aMCI) or AD with mostly mild syndromes or early dementia. The vast majority of patients with aMCI or AD have significant vascular and other comorbidities , leading to diagnosis of mixed etiology MCI or dementia.

Aggressive evaluation and management includes genetic testing for MTHFR, A1AT polymorphisms and in suitable cases APOE genetic testing. Significant comorbidities include vasculopathic MTHFR polymorphisms (58%), B12 deficiency (25%), and obstructive sleep apnea (24% of patients). Management includes genetic counseling, directed vitamin supplementation (B12, folate/riboflavin), treatment of sleep disorders, and usual medications such as acetylcholinesterase inhibitors, memantine and antidepressants/anxiolytics.

In addition to bedside psychometric screens, selected patients received a computerized cognitive battery (CNS Vital Signs) for staging and monitoring. Often given at intake and first revisit (baselining), the test takes 30-40 minutes and allows greater definition of deficits particularly for persons with MCI syndromes with MMSE>23.

Control of the multiple factors affecting behavior and cognition in patients with MCI/dementia syndromes can produce stabilization or improvement in many cases. Monitoring clinical course with computer testing can facilitate assessment and provide a basis for patient and family instruction/compliance with the treatment regimens. Improvement is particularly common with targeted therapy of the vasculopathic MTHFR alleles; examples will be shown.

Most neurodegenerative syndromes are multifactorial, genetic/environmental illnesses. Effective intervention is possible through identifying and treating all complicating factors. [Support by Guardian Angel Thrift Foundation, KB Reynolds Foundation, Duke Endowment].

Disease Model:
The caricature is "single pure entities" with response to single pharmacological interventions. Multiple factors result in heterogeneity and variance even in relatively "pure" genetic cases since these illnesses represent the result of complex environmental and genetic factors further complicated by different responses of patient and caregiver with regard to treatment, compliance and behavioral modulation. We will offer evidence that most cases are in fact multifactorial, most commonly mixed etiology dementias with AD and vascular component . As aggressive evaluation and management is initiated, the key issues are tracking the clinical trajectory of patients and continuing to address both primary and secondary factors

Practice Model:
The model was based on team approach with physician, physician extender (physician associate), medical social worker (currently an RN with home health experience), and office staff. Evaluation and treatment approaches, including diagnostic categories have been presented in previous publications. This mutli-person, multi-visit approach is best suited to neurodegenerative disorders where there is most often need and presence of a second family member, importance of behavioral inventory at home and not merely clinic, and the clinician.

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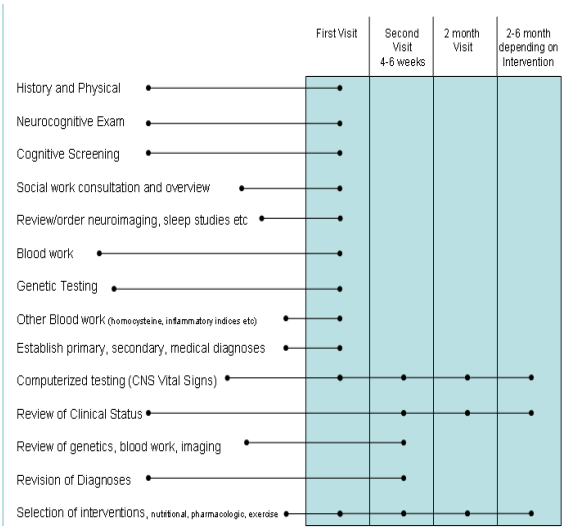
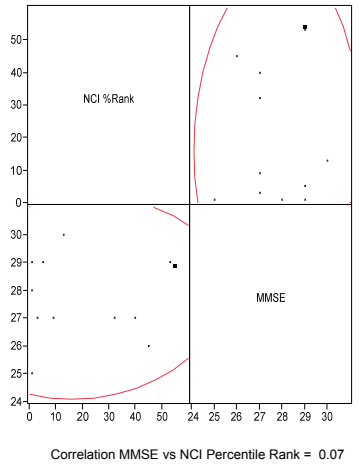




Correlation MMSE vs NCI Percentile Rank = 0.07

Summary

1) Most cases of MCI/dementia have multiple factors, particularly vascular.

2) Factors that can be identified include sleep disorders, vasculopathic factors including diabetes, dyslipidemias, MTHFR alleles (homocysteine metabolism), nutritional.

3) Aggressive evaluation will often include genetic testing to help in differential diagnosis and treatment selection

4) Treatment will then involve multiple therapies and interventions

5) Staging and monitoring can be assisted by cognitive testing at relatively frequent intervals, including short screens such as MMSE or MOCA forms.

6) Finer detail ("granularity") can be revealed using computer cognitively testing such as here illustrated by CNS Vital Signs battery. Test can be administered by support personnel, takes 30-40 minutes, and has alternate forms. Most patients with high school education and reasonable exposure to computers can handle testing. Familiarity and practice effects can be dealt with by leading in with two baselines prior to monitoring.

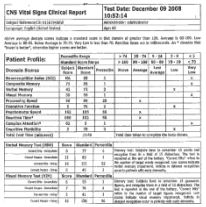
7) MCI and dementia are treatable disorders, involving complex interactions of genes-environment including behavioral responses and life practices of patient and caregiver.

8) Clinical stability and improvement should be sought for assiduously by dealing with all reasonable treatable factors impacting behavior and cognition.

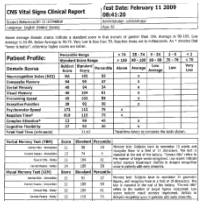
	White male presenting at age 60 with memory problems
MRI	Normal MRI
OPSG	OSA
Genetics	APOE not done MTHFR gene C677T/C677T Homozygote
Initial Dx	Amnestic MCI
Final Dx	Amnestic MCI, possible early AD
Secondary Dx	OSA/UARS
Medical Dx	N/A
Therapy	CPAP for OSA
Meds	Metfolate 3200 mcg/day Omega 3 2000 mg qd

Summary: 60 year old man presenting with significant memory and concentration problems in MCI range, onset age 57. Intact ADL and IADL, but disabling problems in job performance. Work-up reveals OSA/UARS long-standing and vasculopathic MTHFR alleles C677T/C677T. Treatment goals: CPAP treatment, metfolate for MTHFR alleles, omega-3 supplementation, exercise. Follow-up over 2.5 years with stability. CNS VS allowed fine characterization of clinical course, including apparent variation due to compliance with therapy. Complex attention remained impaired, but attentional domains showed ABAB response to metfolate supplementation, and memory domains also responding, possibly more related to CPAP compliance. Patient and wife positively influenced by revelation of testing performance - useful in demonstrating probable effects of compliance. Next steps: probable genetic typing for APOE and consideration of additonal therapies: AChEI, memantine, axona.

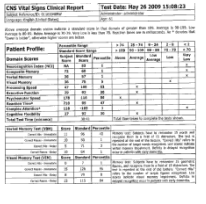
MMSE 25



MMSE 29



MMSE N/A



MMSE 26

MMSE 27

MMSE 27

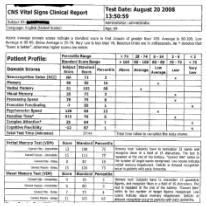
	White female presenting at age 68 with memory problems
MRI	Moderate subcortical vascular disease
OPSG	PLMS
Genetics	APOE 3/4 MTHFR gene C677T/A1298C compound heterozygote
Initial Dx	Non amnestic MCI
Final Dx	Early AD with vascular components
Secondary Dx	PLMS
Medical Dx	Possible nutritional compromise Ethanol Dyslipidemia
Therapy	PLMS treatment Taper and D/C alcohol
Meds	Metfolate/riboflavin for MTHFR Simvastatin Gabapentin 600 hs for PLMS Omega-3 2000 mg qd

Summary: 68 year old woman presenting with significant memory and concentration problems in MCI range, onset age 65. Intact ADL and IADL, but intermittent problems in memory and concentration noted by friends and family. Work-up reveals PLMS and vasculopathic MTHFR alleles C677TA1298C. Treatment goals: PLMS treatment, omega-3 supplementation, exercise, treatment of MTHFR alleles. Follow-up over 2.25 years with stability/improved MMSE. CNS VS allowed fine characterization of clinical course, including improvements in performance. Patient and husband positively influenced by revelation of testing performance - useful in demonstrating current status since MMSE relatively stable. Next steps: emphasis of nutritional factors.

MMSE 29

MMSE 29

MMSE 27



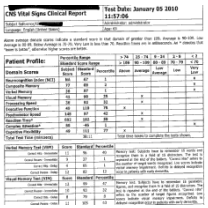
MMSE 30

	White male presenting at age 63 with memory problems
MRI	Moderate subcortical vascular disease
OPSG	OSA/UARS
Genetics	APOE 4/4 MTHFR gene C677T/wt Heterozygote
Initial Dx	Amnestic MCI
Final Dx	Early AD with vascular components
Secondary Dx	OSA/UARS
Medical Dx	B12 deficient autoimmune thyroid disease Dyslipidemia
Therapy	BiPAP for OSA/UARS
Meds	Donepezil 10 mg qd Memantine 10 mg bid Simvastatin Levothyroxine suppression of AITD Omega-3 2000 mg qd

Summary: 63 year old man presenting with significant memory and concentration problems in MCI range, onset age 60. Intact ADL and IADL, but disabling problems in job performance and memory. Work-up reveals OSA/UARS and "normal" MTHFR alleles C677T/wt, also AITD, B12 deficiency. Given wm disease, (-) work-up for MS. Treatment goals: biPAP treatment, omega-3 supplementation, exercise, treatment of AITD. Follow-up over 1.5 years with stability. CNS VS allowed fine characterization of clinical course, including recent decline in performance, Patient and wife positively influenced by revelation of testing performance - useful in demonstrating current status since MMSE stable. Next steps: omit biPAP to see if difference w/r sleep efficiency.. .

MMSE 29

MMSE 28



MMSE 27

Clinical experience at Falls Neurology and Memory Center

Patient population:
2584 total consecutive patients since 7/2007 to date
-1770 patients over age of 50 years
-1023 or 57.8% disorders of memory or concentration or neurodegenerative disor

Distribution of diagnoses:
-Mild syndromes: CIND 0.9%, adult ADD 1.4%,
-aMCI / AD syndromes: aMCI 18.6%, AD 4.1%, ADVD 14.7%, ADPD 2.3%, LBD 0.5%
-Non-AD syndromes: naMCI 7.8%, FTD/FTDPD 4.5%, PD 5.8%, PPA 4.2%, PSP 0.3%, VD 1.5%

Gender distribution: 61% female Average follow-up: 2.0 years
Complicating secondary medical or anatomical diagnoses all patients:
-Obstructive sleep apnea - 24.3%
-PLMS/RLS – 7.0%
-REM-BD – 2.3%
-Adult onset diabetes - 25.7%
-Coronary artery disease (Afib, CABG, stenting,…) – 22.3%
-B12 deficiency - 18.7% new, 6.8% additional cases previously treated

White matter abnormalities – ca 70% of cases

Genetic testing:
A1AT: PiMM 84.5%, PiMS 9.5%, PiMZ 3.6%, PiFM 1.3%, other 1.1% (n=1756)
MTHFR: wt or single mutation– 58.6%, C677Tx2 12%, A1298Cx 2 8.4%, C677T/A1298C 21% (n=1725)
C282Y: C282Y/+ 13.3%, +/+ 86.8%, C282Y/C282Y 0.9% (n=659)
APOE: E44 13.4%, E34 42.7%, E33 34.6%, E24 1.7%, E23 7.7% (n=239)

[A1AT = alpha1-antitrypsin; MTHFR = methylene tetrahydrofolate reductase; C282Y = locus for hemochromatosis mutation; APOE = apolipoprotein E]

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