

Neuropsychiatric Symptoms in Mild Cognitive Impairment

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Overview

- Behavior abnormalities - ubiquitous phenotypic expression of neurodegeneration
- Frontosubcortical circuits and behavioral abnormalities
- Behavioral disturbances in Alzheimer's dementia (AD)
- Behavioral abnormalities in mild cognitive impairment (MCI)

Neurodegenerative diseases

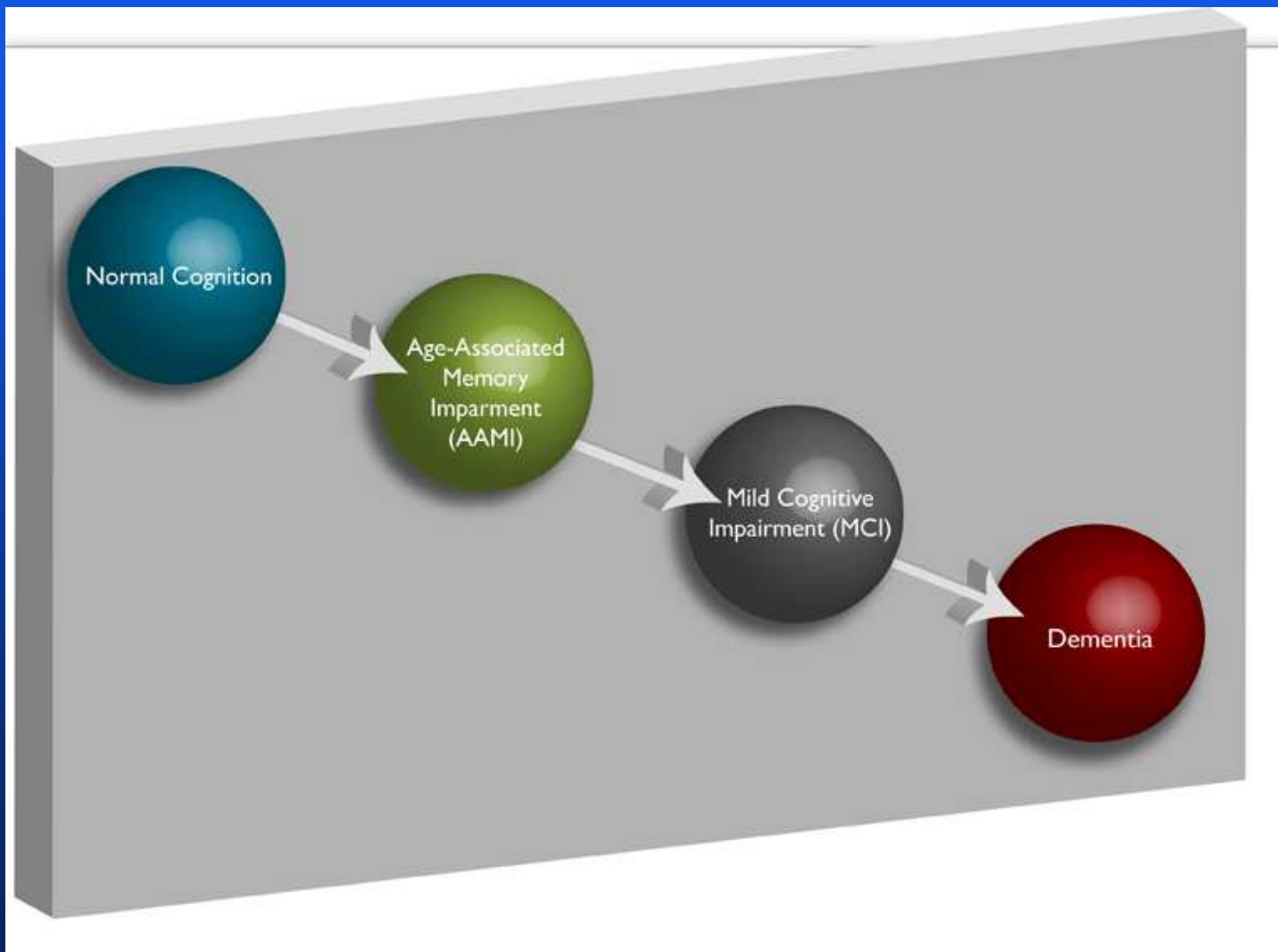
- Similar pathophysiology
- Clinical features
 - cognitive
 - behavioral
 - movement disorder

Phenotypic expression of proteinopathies

Protein	Disease	Common phenotype
A β	AD	Dementia, neuropsych
	Mixed DLB	Dementia, parkinsonism, neuropsych
α -synuclein	PD	Parkinsonism, neuropsych, +/- dementia
	DLB	Dementia, parkinsonism, neuropsych
	MSA	Parkinsonism, dysautonomia, cerebellar, neuropsych
	NBIA	Chorea, dystonia, spasticity, dementia, neuropsych
τ	AD	Dementia, neuropsych
	FTD	Dementia, neuropsych
	CBGD	Parkinsonism, dementia, neuropsych
	PSP	Ocular dysmotility, parkinsonism, dementia, neuropsych
	Dementia of Guam	Dementia, parkinsonism, ALS, neuropsych

Neuropsych = neuropsychiatric features

The Aging-Dementia Cascade



Prevalence of Behavioral Abnormalities in MCI

- Epidemiological studies – 43-51 %

Lyketsos, 2002 and Geda, 2008

- Tertiary centers – 35-75%

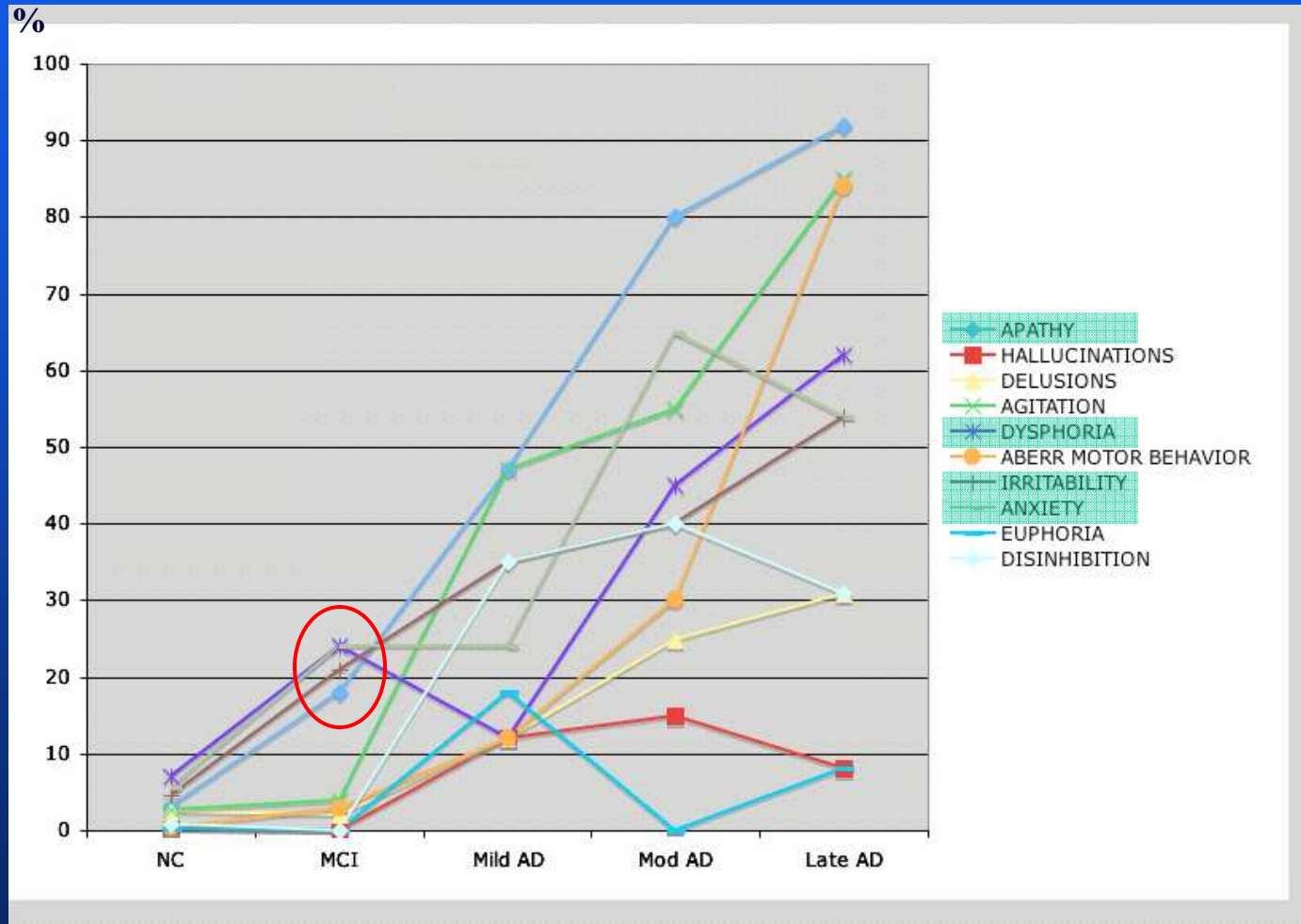
Geda, 2004 and Hwang, 2004

- Non-US studies confirm the high prevalence of behavioral abnormalities in MCI

Muangpaisan, 2008

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- Most prevalent symptoms – depression, apathy, anxiety and irritability

Most Common Behavioral Disturbances in MCI



Adapted from Hwang et al, 2004; Baquero et al, 2004; Lyketsos et al, 2002 and Mega et al, 1996

Factors Affecting Behavioral Symptoms in MCI

- Cognitive impairment associates with higher prevalence of behavioral features
- Functional decline associates with greater prevalence of all behavioral features

Behavioral abnormalities in MCI

- MCI subjects show significantly higher frequency of behavioral symptoms relative to cognitively normal elderly
- The presence of behavioral features increases the odds for MCI
 - Apathy - odds ratio (OR) 4.5
 - Agitation - OR 3.6
 - Anxiety - OR 3.0
 - Depression - OR 2.8
 - Delusions - OR 8.1 (but low prevalence in both cohorts)

Geda, 2008

MCI Subtypes

- Amnestic MCI
 - AD
 - Dementia with Lewy bodies (DLB)
 - Vascular dementia (VaD)
- Nonamnestic MCI
 - Frontotemporal dementia (FTD)
 - DLB
 - VaD
 - Parkinson's disease dementia (PDD)

Petersen, 2001; Winblad ,2004; Jicha, 2006

Prevalence of Behavioral Symptoms in Amnestic vs. Nonamnestic MCI

- Korean tertiary center study of 382 community-dwelling elderly meeting criteria for MCI
- Amnestic MCI (N=217)
 - Depression 20.3%
 - Sleep disorders 18%
 - Irritability 16.6%
- Nonamnestic MCI (N=165)
 - Depression 18.8%
 - Sleep disorders 18.8%
 - Irritability 7.9%
- No significant difference between the subtypes

Lee, 2008

One US tertiary center study disagrees reporting significantly higher prevalence of behavioral symptoms in amnestic vs. nonamnestic MCI

Edwards, 2009

Why The Similarity?

- Amnestic MCI
 - AD - apathy, agitation, irritability, depression
 - DLB - apathy, depression, delusions, hallucinations
 - VaD - agitation, depression, apathy, anxiety
- Nonamnestic MCI
 - FTD - apathy, disinhibition, agitation, aberrant motor behavior
 - DLB - apathy, depression, delusions, hallucinations
 - VaD - agitation, depression, apathy, anxiety
 - PDD - apathy, depression, delusions, hallucinations

Fronto-subcortical circuits

DLPF circuit

1. DLPF Cx
2. Caudate
3. Striatum
4. Thalamus

Anterior Cingulate-subcortical circuit

1. Anterior Cingulate
2. Nucleus Accumbens
3. Striatum
4. Thalamus

Orbitofrontal circuit

1. Orbitofrontal Cx
2. Caudate
3. Striatum
4. Thalamus

Dorsolateral Prefrontal Circuit

Planning/regulation

Organization of behavior

Working memory

Integration sensory input /emotion

Depression

Anxiety

Irritability/agitation

Disinhibition

Euphoria

Psychosis

Anterior Cingulate Circuit

Emotional awareness

Emotional processing

Goal-oriented behavior

Apathy

Depression

Disinhibition

Psychosis

Orbitofrontal Circuit

Eval pos/neg outcomes

Selecting behavioral responses

Detection of performance errors

Social compartment

Interpretation of social cues

Disinhibition

Antisocial behavior

Euphoria

Psychosis

Depression

Behavioral symptoms increase the likelihood for conversion to MCI and AD

- Depression

- Depressed NC from the Cardiovascular Health Study have OR =2.0 for conversion to MCI during 6 year follow up
Barnes, 2006 (also confirmed by Stepaniuk, 2008)
- Several US and non-US studies have confirmed depression as a risk factor for future AD

Copeland, 2003 and Gabryelewicz, 2004

- Anxiety

- MCI with anxiety symptoms have OR=1.8 for conversion to AD over 3 years

Palmer, 2007

Behavioral symptoms increase the likelihood for conversion to MCI and AD

- Apathy

- Higher prevalence MCI converters vs. nonconverters

Robert, 2006

- Higher likelihood for conversion in MCI with vs. those without apathy

Robert, 2008 and Stepaniuk, 2008

- Agitation is associated with faster functional decline

Copeland, 2003

Conclusions

- Behavioral abnormalities are a ubiquitous feature of neurodegeneration
- The prevalence of behavioral abnormalities increases with AD progression
- Behavioral abnormalities are exceedingly common in AD and its pre-dementia state (MCI)

Conclusions

- Behavioral symptoms increase the likelihood of underlying AD type pathology in patients presenting with MCI
- Amnestic and nonamnestic MCI share a common behavioral profile