Depression and cognitive decline in later life: cause, consequence or co-morbidity?

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No conflicts to declare

Learning Objectives

- To understand the complex interplay between depression and cognitive decline in later life.
- To be able to assess and identify cognitive dysfunction in the context of depression.
- To understand the implications which associated cognitive dysfunction has for clinical care and treatment decisions.

A typical case……

- 71 Female
- Widowed 10 years
- Living alone
- Presents with daughter
- Diminished motivation
- Sleep disturbance
- Reduce appetite & weight loss
- C/o back pain/non specific abdominal pain
- Sad….tearful
- Negative thoughts..
- “what’s the point?”
A typical case....

Collateral
- Lives independently
- More withdrawn, low mood & worse self care in last 3/12
- Occasional forgetfulness (particularly last 3/12), medication adherence?
- No other risk issues

Past History
- No previous history of MDE
- Anxious personality
- Bereavement reaction
- Hypertension/OA/TIA
- Amlodipine, HCTZ, aspirin, Acetaminophen prn

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Clothes unchanged, anxious, tearful
Subjectively sad & objectively depressed
Some hope, occasional passive death wish, no suicidal planning or intent
Somatic symptoms but no delusional ideation/ perceptual abnormalities
Unsteady tandem gait, no parkinsonism or focal neurological signs

Daughter has questions...
- Is my mother developing dementia?
- Did depression cause this & will it get better as depression resolves?
- Is the depression treatable?

Cause, consequence or co-morbidity?
- Does depression cause cognitive decline...
- Is it the other way around.....
- Or both?
It is not a “normal part of aging”

Cognitive impairment in non-demented older adults with depression is more common than you think!

Approximately 50 - 60% of non-demented older adults attending secondary care with depression have significant cognitive impairment (Butters et al., 2004)(Lee et al; 2007)

From the Department of Psychological Medicine, University of Durham, England.

PSEUDO-DEMENTIA
L. G. Kiloh

"In these patients the picture of dementia may be very closely mimicked and they may be in danger of therapeutic neglect and perhaps of unnecessary neurosurgical investigations"
A case of mistaken identity…

- Dementia developed more often in the depressed group with "reversible" dementia (43%) than in those with depression alone (12%) (Alexopoulos et al., 1993).
- 71.4% with "pseudodementia" converted to dementia compared to only 18.2% in the cognitively intact group over 5 – 7 yr f/u (Sáez-Fonseca et al., 2007).

Longitudinal course

- Many older adults with baseline cognitive impairment remain impaired despite remission of depressive symptoms (Bhalla et al., 2006) (Kohler et al., 2010).
- Episodic memory and executive function may partially improve following treatment. Older age, later age of onset, higher vascular risk scores & more WMHs predicted less improvement in executive function & processing speed (Barch et al., 2012).
- Among depressed older adults who did not display mild cognitive impairment at baseline 23% were found to develop cognitive impairment one year later (Bhalla et al., 2006).

Late-life depression and risk of vascular dementia and Alzheimer's disease: systematic review and meta-analysis of community-based cohort studies

- Depression with first onset in later life is less likely to be associated with a family history and more likely to be associated with cognitive impairment (Krishnan et al., 2004) (Gallagher et al., 2011).
- Five year follow up of 451 non demented older adults with depression found that late onset depression with executive dysfunction (both major depression & minor depression) was associated with greatest risk of conversion to dementia (Vilalta-Franch et al., 2013)

Who is at greatest risk?

- All-cause dementia (1.85, 95% CI 1.67–2.04, P 0.001)
- Alzheimer’s disease (1.65, 95% CI 1.42–1.92, P 0.001)
- Vascular dementia (2.52, 95% CI 1.77–3.59, P 0.001)
but is depression a true risk factor?

- Depression symptoms are associated with the development of AD, even in families where first depression symptoms occurred more than 25 years before the onset of AD (Green et al., 2003).

Depression may behave as both a prodromal symptom and a true risk factor for Alzheimer’s dementia.

Meta-analysis (9 case control & 11 cohort studies) confirmed a history of depression associated with increased risk of AD in later life.

Interval between diagnosis of depression and AD was positively related to increased risk of AD. (Ownby et al., 2006)

Dose response...

Each episode associated with a 14% increase in risk for all-cause dementia.

A 10% reduction in depression prevalence could potentially result in about 326000 fewer AD cases worldwide and 68 000 fewer cases in the US.
How might depression & cognitive decline be linked?

- Cerebrovascular disease
- Increased beta-amyloid?
- Hippocampal atrophy (glucocorticoid excess)
- Diminished reserve via other mechanisms?

Incident cardiovascular disease

- 11 studies (n = 36,000). Clinical depression (OR 2.69) > depressive mood (OR 1.49) incident MI/coronary death (Rugulies et al., 2002)
- 28 studies. (n = 80,000). OR 1.6 (Van der Kooy et al., 2007)
- Smoking OR 1.25 – 2.5 (passive – ‘active’ smoking)

‘Vascular depression’

- WMHs predict incident or persistent depression

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<th>Depression (Continuous)</th>
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<td>OR</td>
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<tr>
<td>Coronary vascular disease</td>
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<td>Cerebro-vascular disease</td>
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<td>Any cardiovascular disease</td>
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Table 2: Association between depressive symptoms and case level depression according to type of cardiovascular disease (*adjusted for age, gender, education, smoking, physical activity, alcohol intake, raised cholesterol, hypertension and diabetes).

(Gallagher et al., 2013)
Disconnection hypothesis

- Global cerebral WMH severity is less relevant than damage to specific fiber tracts and neural circuits.
- WMH in the cingulum bundle, uncinate fasciculus and superior longitudinal fasciculus (Sheline et al., 2008, Taylor et al., 2011, Dalby et al., 2010).

What about amyloid?

“Amyloid associated depression”

- High plasma AB40:AB42 ratio & greater memory impairment (Sun et al., 2008)
- 3 of 6 patients with treated major depression & MCI were “amyloid positive” (Butters et al., 2008)

Increased Hippocampal Plaques and Tangles in Patients With Alzheimer Disease With a Lifetime History of Major Depression

Michael A. Rapp, MD, PhD; Michal Schneider-Beer, PhD; Hillel T. Grossman, MD; Mary Sano, PhD; Daniel P. Perl, MD; Dushyant P. Purohit, MD; Jack M. Gorman, MD; Vahram Haroutunian, PhD

- Patients with AD and a history of depression exhibited more rapid cognitive decline than patients without a history of depression.
- Both stress and exogenous glucocorticoids increase β-amyloid production in rodent models of AD (Green et al., 2006)

Depression has been associated with faster rate of decline in hippocampal volume (den Heijer et al., 2011)

Meta-analysis 32 studies: Smaller hippocampal volume in those whose duration of illness was longer than 2 years or who had more than 1 disease episode (Mckinnon et al., 2009).
Other possible mechanisms:

- Trophic factors (BDNF)
- Inflammatory activation
- Oxidative/nitrosative stress (Moylan et al., 2013)

The case of need...

We need interventions to reduce cognitive decline in at risk groups. It is not clear which mechanisms mediate the relationship between depression & cognitive decline.

Modifiable risk factors for cognitive decline would be important therapeutic targets in older adults with depression.

Modifiable risk factors & cognitive decline

- 7666 Community dwelling older adults (English Longitudinal study of Ageing)
- 5590 (73.5%) follow up median 47 months
- Excluded those with known dementia/cognitive impairment
- Depressive symptoms (CESD 8 item)

(Gallagher et al., 2015, submitted Journal of affective disorders)
Cognitive Measures
- Delayed recall: 10 words from Health & Retirement Study
- Verbal fluency: Animals in 60s

Nurse Assessment
- Waist measurement
- Blood pressure
- Blood test (CRP, lipids, glucose)
- Metabolic syndrome (IDF)

Analysis
- Descriptive statistics & regression models
- Mediation (Barron & Kenny)

Depressive symptoms independently predicted decline in recall & fluency

Partial mediators
- Physical inactivity ($z = 2.9, p = 0.004$)
- Inflammation ($z = 2.5, p = 0.012$)
- Hypertension ($z = 2.1, p = 0.03$)
- Diabetes ($z = 2.2, p = 0.03$)
- Smoking ($z = 2.2, p = 0.02$)

Did not mediate
- Metabolic syndrome
- Central obesity
- Low HDL, LDL
- Triglycerides

**Table 1**: Socio-demographic and clinical characteristics according to presence or absence of depression (CESD ≥ 4) at baseline.

### Analysis

**Table 2**: Depressive symptoms as a predictor of decline in delayed recall in regression models

<table>
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<tr>
<th>Model</th>
<th>B</th>
<th>95% CI</th>
<th>p</th>
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<tr>
<td>Model 1</td>
<td>0.035</td>
<td>0.008 – 0.062</td>
<td>0.011</td>
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<tr>
<td>Model 2</td>
<td>0.032</td>
<td>0.005 – 0.059</td>
<td>0.020</td>
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<tr>
<td>Model 3</td>
<td>0.097</td>
<td>0.074 – 0.121</td>
<td>&lt; 0.001</td>
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(Model 1: Unadjusted model, Model 2: adjusted for age & gender and duration of follow-up Model 3: adjusted for age, gender, duration of follow-up and cognitive status at baseline).
Physical inactivity
Partially mediated decline in both delayed recall & verbal fluency

Inflammation
Partially mediated decline in both delayed recall & verbal fluency

Physical inactivity & inflammation combined
Mediated the relationship between depressive symptoms & cognitive decline (recall & fluency) (B = 0.026, 95% CI - 0.005 – 0.057, p = 0.11)

Summary of findings
- Physical inactivity & inflammation mediated relationship between depressive symptoms & cognitive decline while hypertension, diabetes & smoking also contributed.
- Findings should be replicated & other potential mechanisms of association included.
- Our findings support the proposition that vascular risk factors & physical inactivity should be screened for and addressed in older adults with depression as part of a comprehensive intervention to delay cognitive decline in this vulnerable group.

A 2 year multidomain intervention of diet, exercise, cognitive training, and vascular risk monitoring versus control to prevent cognitive decline in at-risk elderly people (FINGER): a randomised controlled trial

Figure 2: Change in cognitive performance during the 2 year intervention
(Ngandu et al 2015)
Implications for treatment...

- Primum non nocere!
- Avoid anticholinergic medications (TCA, paroxetine)
- Do not exacerbate hypo/hypertension (venlafaxine, check BP, trazodone, postural hypotension)
- Interactions with other medications & co-morbidities (Na+, QTc)
- Full treatment response may take longer (Nelson et al., 2008).

Executive dysfunction & treatment

- Executive dysfunction associated with worse response to antidepressants (Lockwood et al., 2002; Alexopoulos et al., 2005; Sneed et al., 2007)
- WMHs predict worse treatment response (Sheline et al., 2010)
- Smaller hippocampal volume predicted slower treatment response (Sheline et al 2012)
- Executive dysfunction associated with greater risk of relapse and recurrence (Alexopoulos et al; 2000)

Psychotherapy?

- Both cognitive behavioral therapy (CBT) and interpersonal psychotherapy (IPT) are effective in older adults with depression including those with cognitive impairment.
- Problem solving therapy can reduce depression & disability in older adults with major depression complicated by executive dysfunction (Alexopoulos et al., 2011).
- Problem Adaptation Therapy (PATH) more effective at reducing depression and disability than supportive therapy in older adults with cognitive impairment (Klosses et al., 2015).
What about exercise?
- SEEDS study: MDE > 65 yrs, remission in 45% of participants in the sertraline group, 73% - 81% of those in sertraline+ exercise groups.

(Murri et al; 2015)

Social interventions
- Supportive interventions can reduce depression in caregivers of patients with dementia (Mittelman et al; 2006)
- Some evidence for interventions which increase social activation (Forsman et al; 2011)

Back to the case……
- Blood work and EKG unremarkable…
- Treated with an SSRI and depression remitted…..
- Medication blister packed & monitored by daughter.
- Care supports at home were increased.

MoCA improved a little from baseline (Global score 21/30 to 24/30, attention and recall improved a little)
- Persisting executive deficits
- Microangiopathic disease on MR
Follow up care…

- Vascular risk factors optimised
  (Collaborative care approach)
- Increase physical & social activation
  (150 mins moderate intensity/week, day program support)
- Regular monitoring of mood & cognition
  (Higher risk of cognitive decline & depressive recurrence)

Concerned daughter….

Q: Is my mother developing dementia?
A: Depression and MCI increase risk but not all individuals develop dementia and we can address modifiable risk factors….

Q: Did depression cause cognitive impairment & will it get better as depression resolves?
A: Cognition may partially improve following treatment but many will continue to have some impairment.
Q: Can you treat the depression?

A: Yes, but it may take a little time and we will need to monitor closely following remission.

Summary

- Bidirectional relationship between cognitive decline and depression in later life.
- Depression is a potentially modifiable risk factor for cognitive decline.
- Cognitive impairment in depression is an important therapeutic target.
- Therapeutic approach to depression in later life necessarily accounts for these intertwined relationships.

“We don’t stop playing because we grow old; we grow old because we stop playing.”

George Bernard Shaw