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Tricky diagnoses:
when dementia is not dementia
and depression is not depression

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When dementia is not dementia

• Definition of dementia
  – Cognitive decline → functional decline
• Not exclusively delirium
• Not an Axis 1 diagnosis such as
  – Depression
  – Schizophrenia (*Dementia Praecox*)
  – Mania
  – Malingering
Depression, apathy & cognition

Depression

Cognitive impairment

Apathy
Depression & cognition

Depression

Cognitive impairment
Cognition during episode of depression

- Deficits = core feature at all ages
  - Memory, executive function, processing speed
- More in older people, if depression more severe

Airaksinen E Psycholog Medicine 2010; 34, 83–91
Cognitive deficits persist after recovery from depression

• related to underlying neurobiological changes (atrophy, DWMH)
• More in elderly, late onset depression

¹ Kohler S et al Psychological Medicine 2010;40:591-602
Older person with cognitive impairment and depression

- Is cognitive impairment secondary to depression?
- Is depression secondary to underlying brain pathology such as dementia?
Depression: risk factor for dementia

- Is it prodrome?
  - 25 year build up of AD pathology
- Is it secondary to depression?
  - Depⁿ → cortisol↑ → temporal lobe atrophy
- Is it secondary to treatment of depression?
  - Unlikely
- Mid-life depression associated with (?)↑ risk
- Late-life depression associated with ↑↑ risk
25-year follow-up of depression

- 71 depressed in-pts (10 deceased) and 50 surgical controls assessed 25 years later
- No signif. differences between depressed pts and controls on any neuropsychological test
- 10 depressed patients, no controls had dementia at follow-up $P<0.01$
- Dementia predicted by older age at baseline
- Vascular dementia was most common type

Dementia: risk factor for depression

- Dementia associated with depression
  - \( \approx 20\text{-}50\% \) people with dementia have depression
- Not associated with recency of diagnosis
  - Suggesting unlikely to be a reaction to diagnosis
- Associated with type of dementia
  - More in subcortical dementia (e.g., Parkinson’s disease dementia, vascular dementia)
  - Suggesting likely link to brain pathology
Risk factors common to both

Depression \[\leftrightarrow\] Dementia

Brain pathology

eg CVD
Vascular dementia with deep white matter hyperintensities (DWMH) +++

FIG 4 MRI scan of CADASIL.
Vascular depression

- Cerebro-Vascular disease predisposes, precipitates or perpetuates depression
- MRI: > DWMHs esp frontal-subcortical
- Cognitive ↓, psychomotor retardation/slowing, apathy, executive dysfunction
- Poorer response to treatment
- Worse prognosis: depression, dementia, death

Krishnan 1988, 1997; Coffey 1990; Alexopoulos 1997; Hickie 1997
Depression & dementia

Clinical features overlap

Depression

Cognitive impairment
Symptoms common to both

- Hamilton Depression Rating Scale-21
  - total possible score of 64
  - Sleep disturbance, agitation, retardation, loss of interest, loss of weight/appetite, loss of libido, loss of energy, lack of insight, paranoid delusions, hallucinations \( \Rightarrow \leq 34 \)
## Bedside Dx: dep^n v dementia

### Depression
- Onset recent, course > rapid
- Family always aware
- PPH, FH of dep >likely to be +ve
- > cognitive Sx, > specific
- Pt highlights failures
- Affect pervasive
- Behaviour incongruent with cognitive Sx eg social skills ↓
- O/E – “don’t know” answers, memory loss, past = recent; memory gaps often

### Dementia
- Longer duration, >gradual
- Family often not aware
- FH of dementia may exist
- Pt. complains less
- Pt. highlights success
- Affect labile, shallow
- Behaviour compatible with cognitive Sx
- O/E recent memory<<past, memory gaps unusual

Wells CE, Am J Psychiatry, 1979 (n = 10, 33-69yo, 9 in-pts, 1 out-pt with pseudodementia)
Pseudodementia
Pseudodementia case

First episode:
- 74yo man with depression resistant to TCA Rx; MMSE 19/30
- Depression treated as inpatient with MAOI
- Recovery from depression; MMSE 30/30
- A case of pseudodementia

One year later, recurrence:
- cognitive impairment, longer time to recover, ECT; cognition did not fully recover
Pseudo-dementia case ctd

Two years later

• Third episode – only partially responsive to ECT, cognitive deficits more pronounced

• MRI reveals multiple DWMH

Three years later

• Dementia, now needs help with ADLs
Pseudodementia

- Wernicke (1934) chronic hysterical state mimicking mental weakness\(^1\)
- Madden (JAMA, 1952): 10% of 300 cases

\(^1\) Snowdon J, Australasian Psychiatry, 2011
Pseudodementia

- Kiloh put term “on the map”¹
  - Dementia very closely mimicked by psychiatric condition
  - Many patients misdiagnosed with depression which was untreated
  - Cures with ECT and antidepressants

¹ Kiloh L, 1961 Acta Psych Scandanavica
Pseudodementia

- Def\textsuperscript{n}: Dx confirmed if cognition recovers when psychiatric condition resolves
- Psychiatric conditions $\rightarrow$ Pseudodementia\textsuperscript{1}
  - Depression
  - Schizophrenia, paraphrenia
  - Mania and bipolar $\Delta$
  - Hysteria
  - Malingering, Ganser syndrome

\textsuperscript{1}Kiloh LG, Acta Psych Scandanavica 1961
Pseudodementia

• Intellectual impairment in patients with primary psychiatric disorder in which the features of intellectual abnormality resemble … those of a neuropathologically induced cognitive deficit.

• This neuropsychological impairment is reversible and there is no apparent primary neuropathological process

Caine ED. Arch Gen Psych 1981; 38:1359-1364
Number of 'pseudodementia' publications: Medline per year

- Number of publications

Diagram showing the number of 'pseudodementia' publications per year in Medline.
The myth of pseudodementia

- Single case, 85yo
- Lifelong history of unipolar depression
- With Rx his verbal IQ 86 → 99, tho’ deficits
- Stressed importance of treating pts with potential reversible depression even if cognitive impairment
- Used term pseudo-pseudodementia

Depression + ‘reversible dementia’

- Alexopoulos GS (1993) followed up 23 in-pts with depression and criteria for dementia vs 34 with depression and no dementia
- Age ≈74 ± 6.7; follow-up ≈33 months
- HRSD On Admission 36.6 vs 27.3 **
- MMSE On Admission 18.6 vs 27.3 ***
- MMSE Discharge 26.4 vs 27.6 (p<0.09)
- Dementia by follow-up 43% vs 12% **; OR 4.69
- Mortality – 35% vs 24% (ns)
Pseudo-pseudodementia

- Cognitive deficits do not completely recover
- Persistent executive dysfunction, visuo-spatial and amnestic deficits
- Neurological signs $\rightarrow$ progress to dementia
- Longer follow-up many of pseudodementia pts. $\rightarrow$ true dementia

Kral 1983; Kral & Emery 1989; Reding 1985; Copeland 1992; Alexopoulos 1993
Kiloh’s pseudodementia patients

- Sachdev (1990) followed up 19/21 Kiloh’s PD pts 2-14 yrs later; two not as did not meet PD
- Pts 26-63 yo at baseline; 6 Sz, 13 Affective Δ
- All those alive followed for ≥ 12 yrs.
- 1 pt’s Dx changed to dementia; 1 pt possible dementia
- Conclusion: study validates clinical utility of pseudodementia
Pseudo or pseudo-pseudodementia

- All cases of pseudodementia were <65 and most had long term psychiatric illness
- All cases of pseudo-pseudo were > 65 and often had late onset psychiatric illness
- Poorer memory performance on delayed word list recall
- Imaging - cortical atrophy, ↑ VBR, ↓ pre-frontal cerebral blood flow, DWMH, CVD

Visser 2000
What is apathy?
Apathy components

- Behavioural: ↓ motivation, initiative
- Cognitive: ↓ drive, ↓ interest
- Affect: ↓ emotional responsiveness
What is apathy?

The apathy spectrum includes reduced:

- initiative
- interest
- motivation
- spontaneity
- affection
- energy
- enthusiasm
- emotion
- persistence

+ blunted affect

LOCAL ELECTIONS

LIB DEM CON LAB APATHY

PUGH
WORLD RECORD
ATTEMPT
AT
APATHY

2006/05/12 13:35
Frequency of apathy

- Apathy associated with neurological, psychiatric, medical, drug-induced & socioenvironmental conditions\(^1\)
- Frequency in neurological disease \(\leq 92\%\)^2
- Dementia & schizophrenia commonest \(^2\)

\(^1\)Marin Seminars of Clinical Neuropsychiatry 1996;1:304-314
\(^2\)Pluck & Brown Journal of Neurol Neurosurg Psychiatry 2002;73:636-642
Frequency of apathy

• Highest prevalences of apathy in
  – Progressive supranuclear palsy\(^1\)
  – Fronto-temporal dementia\(^2\)
  – Severe AD\(^3\)
• Apathy following stroke \(\sim 25\%\)^4

\(^1\)Litvan et al *J Neurol Neurosurg Psychiatry* 1998;65:717-721
\(^2\)Hodges *Neurology* 2001; 56:S6-S10
\(^3\)Mega et al *Neurology* 1996;46:130-135
\(^4\)Brodaty et al *Psychol Med* 2005;35:1707-1716
Apathy & cognition

Cognitive impairment

Apathy
Apathy is most common BPSD in dementia?
BPSD prevalence (%)  Robert S et al, 2005

- Delusion
- Hallucinations
- Depression
- Agitation
- Anxiety
- Euphoria
- Apathy
- Disinhibition
- Irritability
- AMB
- Sleep
- Appetite
Frequency of apathy in dementia

- One of the most challenging, prevalent & persistent behavioural symptoms of dementia
- Occurs in up to 70% of those with AD
- A major clinical feature of dementia with subcortical & frontal pathology
  - Dementia with Lewy bodies
  - Huntington’s disease
  - Vascular dementia
  - Binswanger’s disease

1Starkstein et al European Journal of Psychiatry 2006;20:96-106
2Galvin et al Alzheimer Dis Assoc Disord 2010;24:177-181
3Baudic et al Dementia & Geriatric Cognitive Disorders 2006; 21:316-321
4Staekenborg et al J Neurol Neurosurg Psychiatry 2010;81:547-551
5Caplan Neurology 1995;45:626-633
Apathy in MCI

- In 11.1-39.8% of cases\(^1\)
- Intermediate between older normal controls & AD\(^2\)
- Predicts a higher rate of conversion to AD\(^3\)

\(^1\)Lyketsos et al *JAMA* 2002;288:1475-83
\(^2\)Crocco & Lowenstein *Current Psychiatry Reports* 2005;7:32-36
\(^3\)Robert et al *Clin Neurol Neurosurg* 2006;108:733-736
Apathy & dementia

Apathy increases with severity and duration of dementia

Dementia severity
Diagnosis

• Lack of standardised diagnostic criteria\(^1\)
• Difficult for family caregivers to identify & quantify \(\Rightarrow\) under-reporting\(^2\)
• Differentiate lack of motivation rather than cognitive impairment \(^3\)

\(^1\)Starkstein et al *European J Psychiatry* 2006;20:96-106
\(^3\)Marin *Am J Psychiatry* 1990; 147:22-30
\(^4\)Lanctot K et al, Alz & Dementia, 2016 in press
How do we diagnosis apathy?

• History
• Clinical impression
• Apathy rating tools
  – Apathy Evaluation Scale (AES) ¹
  – Apathy Index²
  – Apathy Inventory³
  – Apathy Scale⁴
  – Structured Clinical Interview for Apathy (SCIA)⁵
  – Dementia Apathy Interview and Rating (DAIR) ⁵
  – Lille Apathy Rating Scale (LARS)⁵

¹ Marin RS et al Psychiatry Res 1991;38:143-162
² Mayo et al Stroke 2009;40:3299-3307
³ Robert et al IJGP 2002;17:1099-1105
⁴ Starkstein et al Euro J Psych 2006;20:96-106
⁵ Lanctot KS Alz & Dementia 2016, in press
How do we diagnosis apathy?

• Apathy items in behavioural scales
  – NPI
  – Behaviour and Mood disturbance Scale
  – Clifton Assessment Procedures for the Elderly
  – Frontal Behavioural Inventory

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5Cummings et al Neurology 1994;44:2308-14
6Neville & Byrne Collegian: J Royal College of Nursing, Aust 2001;20:166-172
Depression & apathy & cognition

- Related to but distinct from depression & dysphoria\(^1\)
- Symptoms overlap

\(^1\)Marin et al *J Nerv Ment Dis* 1994;182:235-39
Depression → apathy?

• Apathy common in depression
• 3 items in Geriatric Depression Scale:
  – Have you dropped many of your activities or interests?
  – Do you prefer to stay at home, rather than go out and do things?
  – Do you feel full of energy?
Depression → apathy?

• 2 items in Hamilton
  – Loss of interest, lack of activity in work or hobbies
  – Decreased energy
• When depression lifts apathy improves

BUT …

• Apathy can occur independently of depression
• Depression can occur without apathy
Depression & apathy & cognition

- Apathy > associated with right frontal subcortical circuits
- Depression with left
- After stroke as > CVD
  - overlap between apathy & depression increases
  - overlap between apathy & cognition increases

Withall A, Brodaty H... Sachdev P
Int Psychoger, 2011;23:264-273
Distinct from depression

• Related to but distinct from depression & dysphoria

• Symptoms overlap

• Association between apathy & cognitive impairment (esp. executive function) stronger in apathy than depression

## Apathy vs Depression

<table>
<thead>
<tr>
<th>Apathy</th>
<th>Depression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lack emotion</td>
<td>Sad, tearful</td>
</tr>
<tr>
<td>Don’t care</td>
<td>No point to life</td>
</tr>
<tr>
<td>Not suicidal</td>
<td>May be suicidal/ “rather be dead”</td>
</tr>
<tr>
<td>Not usually anxious</td>
<td>May be anxious</td>
</tr>
<tr>
<td>Vegetative Sx absent</td>
<td>Vegetative symptoms</td>
</tr>
<tr>
<td>usually except lose</td>
<td>– Sleep, appetite, weight, libido</td>
</tr>
<tr>
<td>interest in food/sex</td>
<td></td>
</tr>
<tr>
<td>No sadness ‘transmits’</td>
<td>Clinician ‘feels’ sadness</td>
</tr>
<tr>
<td>AD Rx: Poor response</td>
<td>Rx: Moderate response</td>
</tr>
</tbody>
</table>
Symptoms in common

- Lack interest
- Lack initiative
- Lack motivation
- Decreased libido
- Decreased concentration
- Less energy
Secondary apathy

- Quiet delirium
- Medical ∆ - infection
- Medication side effects can initiate, maintain or imitate apathy\(^1,2\)
  - antipsychotics
  - antidepressants
  - neuroleptics

\(^1\)Colling *J Gerontol Nurs* 1999;25:27-32
\(^2\)Barnhart et al *Journal of Psychiatric Practice* 2004;10:196-199
When depression is not depression
Pseudodepression

Apathy misdiagnosed as depression

• Wife: *My husband is depressed, doctor*
• Dr: “How do you know he is depressed?”
• Wife: “He just sits all day and does nothing”
• Dr: “Is he sad, does he cry, does he say life has no meaning?”
• Wife: “*No he does not say anything unless I ask him. He just sits!*”
Pseudo-depression case

- 67 yo man hit by a car \(\rightarrow\) closed head injury
- “Depd” \(\rightarrow\) Multiple antidepressants, group and individual therapy, ECT – no better
- Five years later, referred w Treatment Resistant Depression
- His P/Sx: *I’ve lost the need to talk*
- CT brain scan normal, MMSE 29/30
- MRI – frontal pathology
- Neuropsych – frontal executive dysfunction
Pseudodepression

• Apathy often misdiagnosed as depression
• Apathy is common in depression
• Apathy is unresponsive to antidepressants
• Apathy Rx = ChE inhibitors, (Modafinil), methylphenidate
• Apathy and depression may be comorbid

¹Brodaty and Burns, Am J Ger Psychiatry, 2012; 20(7):549–564
Apathy and depression may be comorbid

Depression ↔ Apathy

Frontal – subcortical pathology
Conclusions

- Overlapping syndromes
- Overlapping symptoms
- Common pathologies
- Underlying brain chemistry, pathology differ
- Treatments/management strategies differ

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