From Neurodevelopment to Neurodegeneration: Behavioral Issues

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Objectives

• Discuss factors that contribute to neurocognitive and behavioral changes in those aging with developmental disabilities
• Discuss an approach for the assessment and management of behavioral issues arising from neurocognitive disorders in old age
• Discuss a case example of neurobehavioral change in a patient aging with developmental disability
Faculty/Presenter Disclosure

• Faculty: Dr. Amer Burhan

• Relationships with commercial interests:
  – None
Disclosure of Commercial Support

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• **Potential for conflict(s) of interest:**
  – None
Mitigating Potential Bias

• Not applicable
DSM-5: Neurodevelopmental Disorders

- Group of disorders with onset in early development
- Range from specific deficits in learning, executive control to global impairment in social functioning and intelligence
- Results in impairment in personal, social and occupational function
- Intellectual disabilities, global developmental delay, communication disorders, autism spectrum disorders, ADHD, specific learning disorders, motor disorders, Tic disorders, other
DSM-5: Neurocognitive Disorders

Neurocognitive disorders

- Delirium (acute/reversible)
- Mild or Major NCD (chronic/persistent/progressive)
Delirium

A. Disturbance in attention and awareness
B. Develop over short period and is acute change from baseline
C. Disturbance in other cognitive domains
D. Not better explained by preexistent neurocognitive disorder
E. Evidence of medical/substance/toxin cause
Mild or Major Neurocognitive Disorders

- Acquired decline in one or more cognitive domains from previously higher level of function
- Domains: executive function, learning and memory, complex attention, language, perceptual and motor skills
- With/without significant functional and independence loss
Specification

Neuro-degenerative:
• Due to Alzheimer’s disease (AD)
• Due to Fronto-temporal lobar degeneration (FTLD)
• With Lewy bodies (LBD)
• Due to Parkinson disease (PD)
• Due to Huntington disease (HD)

Brain insult:
• Vascular neurocognitive disorders (VCI)
• Due to Brain injury (TBI)
• Substance and medication induced
• Due to another medical condition
• Due to multiple etiologies
Aging with Neurodevelopmental Disorders

• Physiological changes and vulnerability to delirium
• Cognitive aging/cognitive reserve interaction
• Social changes (e.g. aging parents and siblings)
• Direct link to neurodegeneration
Direct Link to Neurodegeneration

- Down Syndrome—Alzheimer disease (Wiseman 2015)
  - Early onset
  - Increase rate with age (from <5% below 40 to about 70% at 65, doubles every 5 years)
  - No effect of gender or cognitive reserve
  - High cholesterol associated with increased risk but not other lifestyle factors (HTN, atherosclerosis, smoking)
  - Usually present with behavioral symptoms
Direct Link to Neurodegeneration

• Down Syndrome—Alzheimer disease
  – Clinical features:
    • typical changes in memory and cognition but more executive deficits
    • More behavioral issues in early stages (compared to usual AD and dementia in other ID patients) (cooper 1998, Dekker 2015)
  • More neurological issues
    – Seizures (especially myoclonic onset): more aggressive course
    – Gait changes and parkinsonism
Direct Link to Neurodegeneration

• Down Syndrome—Alzheimer disease
  – Neuropathology:
    • trisomy 21, amyloid precursor protein (APP) double dosing
    • While in duplicate APP rare illness penetrance is almost 100%, not in Down Syndrome (possible protective mechanisms on chromosome 21?)
    • Role of cholesterol x APOE-4
APP, PSEN1, PSEN2 FAD mutations

APP

Aβ42 aggregation

Soluble forms of oligomeric Aβ

Deposited Aβ peptide

Aggregate stress

Tau + NFT

Neuronal dysfunction and death

Dementia

APP FAD mutations, trisomy 21

Reitz C. 2012
Direct Link to Neurodegeneration

• Down Syndrome—Alzheimer disease
  – Therapeutics
    • Managing cognitive and behavioral symptoms symptomatically (Prasher 2004)
    • Amyloid modifying therapies (trialed in other forms of genetic Alzheimer disease)
    • Cholesterol management
    • Anti-inflammatory
Other Neurodevelopmental Disorders

• No clear link to neurodegeneration in other common forms of DD like Autism spectrum disorder but effect of aging is becoming more important (Happe 2012)

• Neurobiological (cognitive reserve, white matter integrity), neurophysiological (pharmacokinetics/pharmacodynamics), and psycho-social changes interact with DD in old age
CLINICAL ASSESSMENT OF NPSD
The Neuropsychiatric Inventory (NPI)

- The NPI measures the frequency and severity of behavioral symptoms

  - Agitation/aggression
    - Depression
    - Disinhibition
    - Elation
    - Irritability
    - Anxiety
  - Aberrant motor behavior
  - Hallucinations
  - Night-time behavior
  - Appetite/eating
  - Apathy
  - Delusion

- Total score ranges from 0 (minimum) to 144 (severe)

Cohen-Mansfield Agitation Inventory

- Assesses frequency of 29 problem behaviors rated 0 (never) to 7 (several times an hour), and timing (am, afternoon, evening) over 1 or 2 weeks
- By proxy rating (family, staff)
- Verbal agitated, physically non-aggressive, physical aggressive behaviors

### Cohen-Mansfield Agitation Inventory (CMAI)

**Instructions:** For each of the behaviors below, check the rating that indicates the average frequency of occurrence over the last 2 weeks.

<table>
<thead>
<tr>
<th>Behavior</th>
<th>Never 1</th>
<th>Less Than Once a Week 2</th>
<th>Once or Twice a Week 3</th>
<th>Several Times a Week 4</th>
<th>Once or Twice a Day 5</th>
<th>Several Times a Day 6</th>
<th>Several Times an Hour 7</th>
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<td>1. Hitting (including self)</td>
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<td>9. Hurt self or others</td>
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<td>10. Tearing things or destroying property</td>
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<td>11. Making physical sexual advances</td>
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<td>12. Paces, aimless wandering</td>
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<td>13. Inappropriate dress or disrobing</td>
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# Dementia Observation Scale (DOS)

Use corresponding numbers to record in ½ intervals.

1. Sleeping in Bed
2. Sleeping in Chair
3. Awake/Calm
4. Noisy
5. Restless, Pacing
6. Exit Seeking
7. Aggressive - verbal
8. Aggressive - physical

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<th>YMD</th>
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The **DICE** Approach

- **Describe**
  - Caregiver *describes* problematic behavior
    - Context (who, what, when and where)
    - Social and physical environment
    - Patient perspective
    - Degree of distress to patient and caregiver
  - Provider *investigates* possible causes of problem behavior
    - Patient
      - Medication side effects
      - Pain
      - Functional limitations
      - Medical conditions
      - Psychiatric comorbidity
      - Severity of cognitive impairment, executive dysfunction
      - Poor sleep hygiene
      - Sensory changes
      - Fear, sense of loss of control, boredom
    - Caregiver effects/expectations
    - Social and physical environment
    - Cultural factors
  - Provider, caregiver and team *collaborate to create* and implement treatment plan
    - Respond to physical problems
    - Strategize behavioral interventions
      - Providing caregiver education and support
      - Enhancing communication with the patient
      - Creating meaningful activities for the patient
      - Simplifying tasks
      - Ensuring the environment is safe
      - Increasing or decreasing stimulation in the environment

- **Evaluate**
  - Provider *evaluates* whether “CREATE” interventions have been implemented by caregiver and are safe and effective

Kales et al, JAGS, 2014
Factors

- **Patient factors and unmet needs**: pre-morbid physical and psycho-social characteristics, isolation, sensory deficit, pain, 4 B’s (bowels, bladder, beverage, bottom to top survey), medical and psychiatric illness

- **Caregiver factors**: distress, understanding, skills

- **Environmental factors** (stimulation level, crowding, temperature, lighting, noise, routine, activities available etc.)

Interventions

• Correct the correctable (patient, environment, caregiver factors)
• Education interventions
• Non-pharmacological interventions
• Pharmacological interventions when indicated
Educational Interventions

- Target informal and formal caregivers
- Include:
  - Skill training
  - Psycho-education
  - Academic detailing
  - Communication training
- Generally moderately effective especially academic detailing to reduce inappropriate medication use

Nonpharmacologic Management

• Heterogeneous, modest effect size, need further validation and standardization
• Validation, reminiscence, reality orientation etc
• Activation
  – Social (1:1, pets, validation)
  – Physical (exercise, purposeful activities)
• Sensory
  – Music (individualized is better)
  – Therapeutic touch/message
  – Snoezelen
  – Aroma therapy

Pharmacological Interventions: Antipsychotics

- Statistically significant but modest effect (20-30% over placebo), NNT 5-14, prominent placebo response (30-40%)
- Effect studied is for short term use (up to 12 weeks) BUT NPSD are persistent (especially psychosis, depression and aberrant motor)
- Effect for aggression and psychosis and not for other symptoms of agitation
Safety Concerns with Antipsychotics

- EPS
- Cognitive changes
- Metabolic: weight gain, diabetes mellitus, hyperlipidemia
- Cardiac: QTc prolongation
- stroke
- mortality
Stroke Risk

- NNH= 6 for 1 year use, 37 for 3 month use
- Risk of serious stroke for Risperidone is 2.3 that of placebo and for Olanzapine 1.8 that of placebo
- Typicalis are equivalent to atypicalis

UK committee on safety of medicines 2004
Herrmann and Lanctot, 2005
Gill et al, BMJ 2005
Atypical antipsychotics used “off-label” to treat behavioral disorders in dementia are associated with an 1.6-1.7 increased risk of death compared with placebo.

– Death causes varied: most heart-related (heart failure, sudden death) or infections (pneumonia)

In Canada, Risperidone is “on-label” to treat Sever AD to manage aggression and psychotic symptoms

Schneider et al JAMA, 2005: 15 RCT death rate was 3.5% on atypicals compared to 2.3% on placebo (1.54 OR)

Similar for typicals

FDA warning in April 2005 following an agency review of 17 placebo-controlled trials: Death!


Are Other Psychotropics Effective?

• Recently CitAD trial demonstrated efficacy of citalopram at 30 mg (Cognitive side effects and QT prolongation was a concern)

• Carbamazepine has three small trials showing good effect on aggression and hostility (300-600 mg) though with significant risks (drug-drug interaction, rash, agranulocytosis, cognitive impairment)

• Others with weak evidence but can be used short term (Trazodone, gabapentpine etc)

Porsteinsson et al 2013, Yi-Chun Yeh & Wen-Chen Ouyang 2012
Are Other Psychotropic Drugs Better for Mortality Risk?

• Not really!

• A database study reported on mortality and femur fractures in 10,500 patients admitted to LTC and concluded that typical AP, antidepressants and benzodiazepines carry comparable risk to atypical AP

Huybrechts et al CMAJ 2011
What Happened to Prescription Pattern in LTC in Ontario Since Black-box warning?

Vasudev et al 2015 Am J Geritr Psychiatry
What else Happened?

![Graph showing percentage trends over time for different categories of psychotropic medication use from 2004 to 2013. The categories include: No psychotropics, One class, and Two or more drug classes. The graph illustrates a decrease in the percentage of patients using no psychotropics, a slight increase in the percentage using one class, and a steady increase in the percentage using two or more drug classes. The sources cited are Vasudev et al. 2015 Am J Geritr Psychiatry and A.M. Burhan.]

Vasudev et al 2015 Am J Geritr Psychiatry
Case 1-typical

• 52 year old man with Down Syndrome
• Lived in supportive housing, goes to a workshop in the Sault Area, takes the bus and prepare simple meals independently
• About a year of becoming less interested, more irritable and oppositional, which is a change from baseline
• Started missing the bus as it took him longer to get ready and could not keep track of the time as well
Case2-atypical!

• 60 year old single white female, worked as PSW,

• Married for couple of years a man 30 years her senior (when she was 20) and had one son but he left her after 2 years

• Always lived across the road from her brother who always did every thing to support her, parents lived close-by and always took care of her
Case continue

• Presented with psychotic symptoms and was diagnosed with borderline personality traits, started antipsychotic medications, which was increased rapidly to high dose (4 mg)
• Got acutely confused, agitated and psychotic at home and was taken to the hospital
• Found to have mix bag of UTI, bowel obstruction
• Stopped meds, admitted to general medical, psychiatry won’t do anything with her
• Restrains, ulcers, lost mobility
• BSO involved, we learned that her son had a genetic illness (sister is MD in Alberta)
Diagnosis

• Digeorge syndrome (chromosome 22 deletion) confirmed
• Treated with ECT, better
• Titrated gradually on antipsychotic
• Stabilized
Conclusions

• People with DD are aging more successfully, which brings the challenge in understanding the cognitive and psycho-social changes this population faces
• People with Down syndrome are at a very high risk to develop Alzheimer
• The development of NCD in people with DD can be signaled by change in behavior
• NPSD are complex and require individualized multifaceted approach
• More attention need to be given to the needs of people with DD developing NCD to understand their unique needs