Huntington Disease

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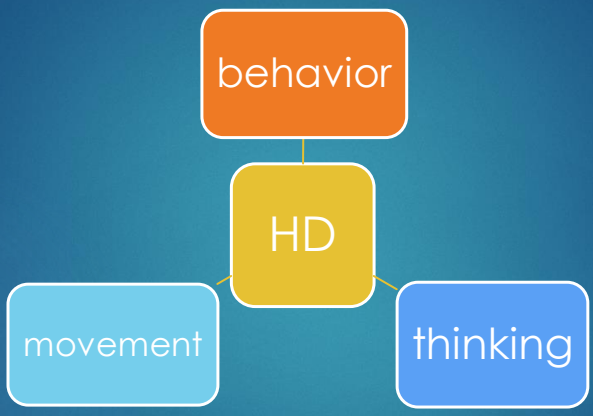
1

Objectives

- Explain the genetic basis for Huntington's Disease and the relationship between genotype and clinical presentation
- Identify cognitive, behavioral, and psychosocial complications of Huntington's Disease
- Formulate a comprehensive plan to help patients, families, and caregivers cope with these complications

2

Overview of HD



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History of HD

Year	Event
1374	"Epidemic dancing mania" described
1686	Thomas Sydenham describes post-infectious chorea
1832	John Elliotson identifies inherited form of chorea
1872	George Huntington characterises HD
1955	HD described in Lake Maracaigo region of Venezuela
1983	Gene marker for HD discovered
1993	HD Gene discovered
2000	Drugs screened for effectiveness in transgenic animal models

Adapted from: https://doi.org/10.1016/S0140-6736(07)60111-1

4

HD Genetics

5

- CAG (glu) repeat on 4p16.3
  - Normal: <27
  - Intermediate:27-35 (prone to expansion)
  - Incomplete penetrance: 36-39
  - Complete penetrance: 40+
- 90% autosomal dominant inheritance
- Age of onset and rate of progression correlated with CAG repeat number
- Presents at any stage of life, usually in early middle age
  - Juvenlie HD – onset before age 20, usually with CAG repeat > 60

5

Epidemiology

- White populations 5-7/100,000 people affected
- Higher in certain areas (Tasmania, Lake Maracaibo) due to founder effect
- Japan 0-5/100,000
- Lower in other areas of Asia, Africa
- More white people have Intermediate CAG repeats (27-35)
- Not thought to confer any advantages (though possibly lower incidence of cancer due to upregulated *TP53*)

6

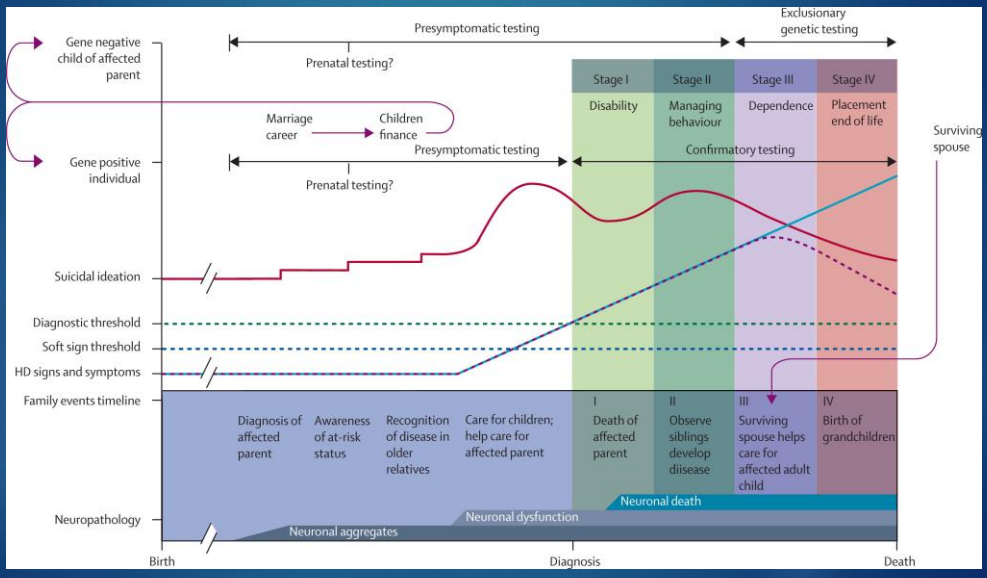
Genetic Testing

- Detect CAG repeats
- Genetic counseling
  - Assess at-risk status
  - Individual reasons for testing
  - What can be done with the results
  - Family planning
  - Assess capacity
- Approximately 1 month wait for results
- In-person disclosure
- Only offered to patients 18 and older

7

Life Cycle

https://doi.org/10.1016/S0140-6736(07)60111-1



8

Pathophysiology of HD

9

- Abnormal accumulation of Huntingtin protein
- Loss of striatal medium spiny neurons
- Marked specificity:
  - Most affected: caudate and putamen with projections to the globus pallidus
  - cortical layers 3,5,6
  - CA1 region of hippocampus
  - Substantia nigra
- Caudate atrophy can be seen on imaging up to 11 years prior to onset of symptoms

9

Movement Disorder

10

- Pre-diagnostic phase:
  - Restlessness, fidgeting noted by family
- Diagnostic phase:
  - Chorea
  - Motor impersistence
  - Incoordination
  - Slowed saccades

- motor example
- rating scale standard

10

Behavioral Disorder

11

- May present with behavioral symptoms:
  - Irritability, anxiety, mood instability
- Common symptoms
  - Disinhibition
  - Suicidal ideation (up to 25% attempt)
  - Apathy
  - Depressed mood
  - Euphoria
  - Aggression
  - Insomnia/sleep phase disturbance
- Less common:
  - Delusions
  - Compulsions
- Rare findings
  - Hallucinations
  - Hypersexuality
- Not linked to motor disease severity

11

KL

- 23 year-old G2P1001 admitted to inpatient psychiatry on 302 for ingesting 4 unknown pills
- Does not engage in interview on admission
- One previous psychiatric admission for homicidal ideation toward her brother and aggression toward police
  - Diagnosed with impulse control disorder and started on citalopram
  - Lost to follow up
- Presented to Magee at 20 weeks gestation to initiate prenatal care and now at 7 months
- No medical history
- Transferred to Magee for episode of unresponsiveness, transferred back to WPH, then discharged home with diagnoses of impulse control disorder and conduct disorder

12

KL

- Presents to WPH again 4 days after discharge; threatening to end her life by terminating her pregnancy by stabbing herself. Says that she "can't stand the kicking."
- Noted to have concrete thought and slow thought processes and given a diagnosis of "probably borderline intellectual functioning"
- Transferred to Magee and delivered via c-section after PPROM
- Noted during this hospitalization to have latency of response, abnormal tone in upper extremities, staring spells, and grimacing
- MRI and other workup recommended but patient and family refused
- Discharged home with baby to live with her mother

13

KL

- 2 months later: brought to WPH on 302 for putting her baby in scalding water.
- Threatened mother with knife when the baby was taken from her.
- Tried to grab taser from police when they arrived
- Did not engage with evaluator
- Now diagnosed with unspecified psychosis
- Noted to have flat affect, poor immediate recall, unable to spell WORLD forward or backward
- Physical exam significant for dystonia, shuffling gait, hyperactive reflexes

14

KL

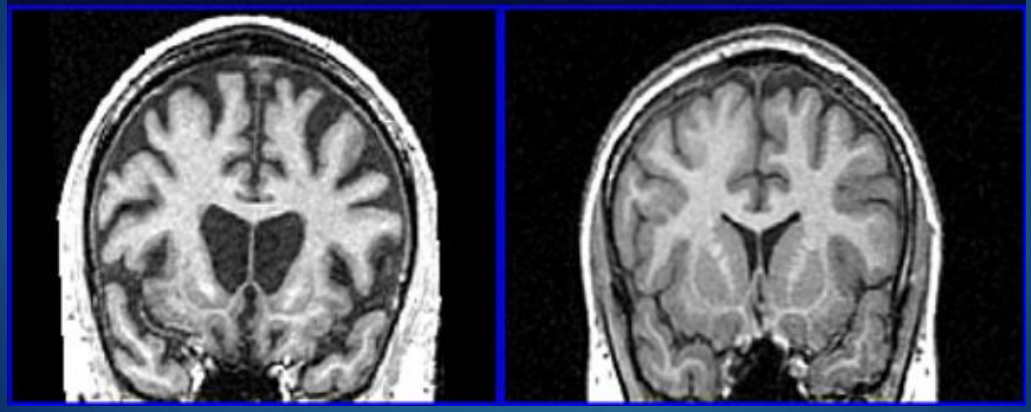
- Family history
  - Mother with schizophrenia
  - Father "died of a psychotic disorder"
- Developmental history
  - Normal until age 14
  - "Straight A" student with decline in high school
  - Started to become more withdrawn, less interested in activities in late adolescence
- Now able to get MRI, labs to r/o HD, Wilson', neuroacanthocytosis

15

MRI findings in HD

HD

Normal



16

KL

- CAG 60
- Mother later found out that K's father had HD
- Referred to HD specialty clinic
  - Haloperidol 5 mg qhs
  - Trazodone 50 mg qhs
- Rapid progression of rigidity and cognitive decline
- Less aggression
- Living in skilled nursing facility

17

Cognitive Disorder

18

- Subcortical frontal dementia
  - Caudate nucleus relays information to and from frontal lobes
- Deterioration in executive function
  - Planning
  - Organizing
  - Learning new skills
- Speech production deteriorates before comprehension

18

Cognitive Disorder

19

- May show difficulty with complex tasks prior to diagnosis
  - Difficulties at work
  - Planning and organizing at home
- Memory generally spared
  - Will show difficulties with memory late in the disease
- Progressive cognitive decline correlated with motor disease severity
  - In contrast to behavioral problems

19

JS

- 14 year old boy referred to HDSA Center of Excellence by pediatric neurology
- Diagnosed with HD by genetic testing at age 7 after showing motor symptoms
  - Inpatient psychiatric hospitalization at age 5 for behavioral disturbance
  - Dx bipolar d/o and ADHD
- Father affected, died in his late 30s
- 5th generation with HD

20

JS

- Presents to clinic with foster family
- Interval History:
  - Recent onset generalized tonic-clonic seizures
  - Difficulty chewing and swallowing
  - Requires wheelchair for mobility
  - Blepharospasm limiting visual ability
  - Prominent dysarthria and hypophonia
  - Increased aggression and disinhibition
  - Compulsive masturbation
  - Cognitive decline – no longer attending school

21

JS

- Exam:
  - Poor attention and concentration
  - Unable to participate in Luria testing
  - Blepharospasm
  - Limited EOM with slowed saccades
  - Marked motor impersistence
    - "milkmaid grip"
  - Walks only with 2-person assist
  - Tone increased throughout
  - Reflexes brisk throughout
  - +myoclonus

22

Westphal variant

- Juvenile onset
  - 10% have sx before age 20
  - 5% before age 14
  - 1% before age 10
- Usual presentation
  - Neuropsychiatric sx
  - Deline in school performance
  - Bradykinesia, rigidity, Parkinsonism
- Later, chorea involving proximal muscle groups
- 50% with seizures
- Faster progression with death ~7 years after movement disorder

23

JS

- Course age 14-16
  - Increased difficulty swallowing 2/2 abnormal movements of tongue, incoordination
  - Tires with eating, meals take up to 90 minutes
  - Eventual move to g-tube with pleasure feeds
  - BMI drops to 16.7
  - Worsening agitation leads to referral to child psychiatry
    - Trials of quetiapine and risperidone lead to worsening agitation
    - Haloperidol titrated to 2 mg q6h with good effect
    - Leuprolide IM q3weeks effective for compulsive masturbation
    - Fluoxetine 10 mg daily for depressed mood/anxiety
  - Abrupt worsening of behavior

24

JS

- Admitted with worsening behavior
  - Urinary retention noted
  - Catheterized and anticholinergics discontinued
  - Haloperidol 2 mg tid prn added
  - Discharged home
- Readmitted with fever to 104, rigidity, CPK >10000
  - Haloperidol discontinued
  - Supportive care + dantroline
  - Scapular fracture found on x-ray, attributed to violent myoclonus
  - Remained delirious after recovery
    - Sedated and unable to interact
    - Agitated and interfering with care
  - Court order for for palliative sedation with agreement of foster family
  - Died 5 days later

25

Psychosocial

- HD affects family systems
  - Onset usually in middle age after patients have had families
  - Affected patients have often seen parents progress through the illness
  - Children care for affected parents
  - Non-affected parent cares for adult affected children
- HD-specific care is hard to find
  - Rare disease
  - Behavioral manifestations make it hard to find and keep caregivers
  - Families/caregivers need support and training

26

SM

- 47 yo woman with onset of motor symptoms at age 39
- Diagnosed gene-positive at age 41 with some clumsiness, falls
- Most bothersome symptoms were depression, irritability
  - Conflict with husband and 7 year-old son
  - Family therapy not helpful
- Impulsivity
  - Threw financial records out on the street outside their house
- Some relief with sertraline
- Progressed to accusing her husband and son of not caring about her and not wanting her to eat

27

SM

- Started to call son's school, other parents and accuse her husband of sexually abusing her son
- CYF investigated and found no evidence to support this
- Pt admitted to WPH due to delusions that were making it impossible for her to function at home, weight loss
- Started on haloperidol and divalproex
- 1st follow up visit: acknowledges that she believed some "odd things" and thinks they were true at the time but are no longer
- Calm and able to enjoy time with husband and family; notably bradyphrenic on exam

28

Life Cycle

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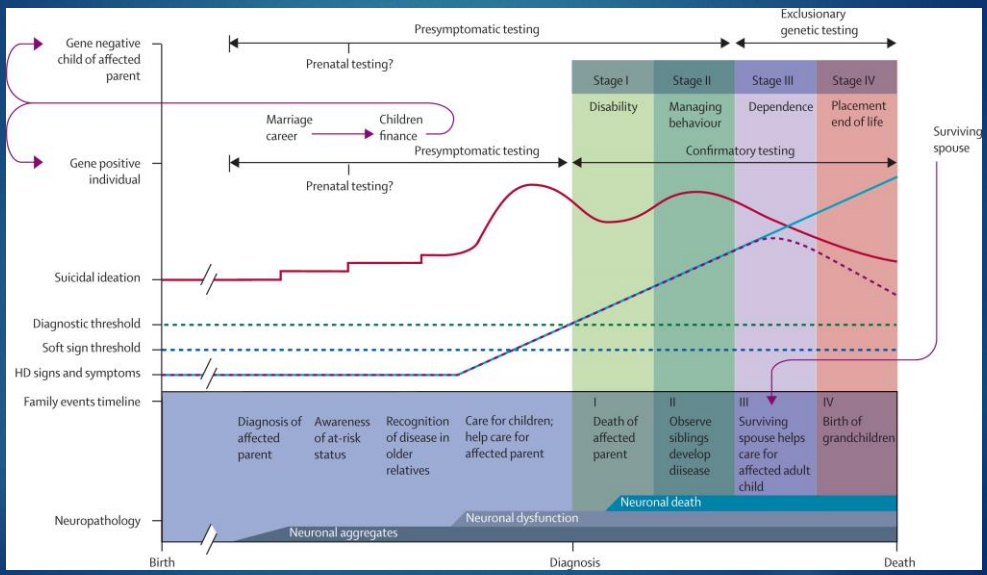


29

Role of the Behavioral Health Team

30

- Treatment of behavioral symptoms
  - Very little evidence base to guide treatment
- Collaborate with neurologist to streamline psychotropics
  - VMAT inhibitors vs D2 blockers
  - Clonazepam for dystonia vs anxiety
- Distinguish cognitive dysfunction from other causes of psychiatric illness
- Advise families on behavioral interventions
- Assessment of readiness for HD testing

30

Psychiatric Assessment of the HD Patient

31

- Full assessment with careful attention to:
  - Family history
    - Who has HD and at what age did sx start
    - What impact did growing up in a household with HD (if applicable) have
  - Trauma
    - Increased risk of victimization
    - Impulsivity and poor judgement
- Past Psychiatric History
  - Previous psychiatric diagnoses – emphasis on early signs of HD
  - Previous psychiatric tx and response
- Centrally active medications
- Substance use
- Risky behaviors
- Legal issues
- Symptoms of depression, demoralization, and/or apathy
- Suicidality

31

TM

- 38-year-old male with Huntington's Disease who presented with chief complaint of insomnia and depression
- Current Psychiatric Symptoms
  - Insomnia
  - Depression with chronic suicidal thoughts
  - Anxiety
  - Intrusive thoughts about childhood
- Pt identified self-medicating his anxiety and insomnia with alcohol use

32

TM

- Family Hx and Personal Hx with HD
  - Father, grandmother and great-grandfather all diagnosed with HD
  - Father presented when he was in late 20s, when pt was around 10
  - Father alive but institutionalized
  - At this point, started to look up early signs of HD and found many symptoms that matched his own
  - Genetic testing after 18, but felt like he "knew" he had HD at age 10

33

TM

- Psychiatric Symptoms
  - Depression since age 10
    - Childhood experiences, embarrassing moments
    - Ruminative thoughts lead to suicidal thoughts chronically; no plan, intent or acts of furtherance
    - One aborted suicide attempt as teenager (standing on bridge)
  - Anxiety
    - Racing thoughts, particularly at night
    - Social component related to HD symptoms
  - Insomnia
    - Difficulty falling asleep and staying asleep
    - Has been seeing sleep specialist, multiple med trials
    - Diagnosed with mild OSA, but does not use dental appliance (removes it when he is infoxicated)

34

TM

- Substance Use Hx
  - Uses alcohol to help fall asleep every night
  - Takes 3-4 shots bourbon/whiskey every night, to point of feeling tipsy/intoxicated
  - No significant change in tolerance
  - Abstinent for 18 months, but felt tired all the time, insomnia out of control and worsened anxiety
  - Does not identify alcohol use as problem, as this is treatment for anxiety and insomnia

35

TM

- Psychiatric Hx
  - No previous inpatient or outpatient treatment; no individual therapy
  - Previous Med Trials: zolpidem, Lorazepam 4 mg, Olanzapine 10 mg, Sonata 10 mg, Doxepin 10 mg, Trazodone, Sertraline 100 mg, 2-3 other antidepressant that he cannot remember
  - Sleep aids not helpful
    - Many taken along with alcohol
  - Antidepressants "work opposite"
    - Doesn't notice an effect while taking, feels better when stopping

36

TM

- Social Hx
  - Lives alone
  - Never been in relationship
    - Interested in having a partner, but inhibited by his HD diagnosis
  - Main supports are mom and brother
    - Both live 5 minutes away
    - Significant conflict
    - Trying to become less dependent on them
  - Disability for HD and Depression

37

TM

Neuro Exam

- VS: Weight 210 lbs; BMI 25.6 kg/m2
- No tremor or notable psychomotor slowing
- CN II-XII grossly intact
- Strength: normal in upper/lower extremities; no cogwheeling or noted rigidity
- Deep tendon reflexes: Slightly brisk throughout
- Coordination: mildly uncoordinated bilaterally with rapid alternating movements without significant slowing; no dysmetria on finger-to-nose
- Tongue protrusion: normal
- No difficulty with Luria testing
- Gait: slightly wider-based, but steady; tandem gait with deviation 1-3 times in 10 steps

38

TM

- Diagnosed with MDD, EtOH use d/o, insomnia (delayed sleep phase disorder?)
- Trial of Li ineffective as augmentation for mood
- VPA partially helpful
- Sleep medicine
  - Considered EtOH to lorazepam cross-taper
  - Considered Xyrem

39

Substance use and HD

- Mixed data regarding prevalence of substance use disorders in HD population
  - Challenge with temporal relation: substance use often starts at younger age than is typical for HD onset
- Rates of alcohol use disorder appear comparable to general population
  - *King 1985, Jensen et al 1993, Ehret et al 2007*
- Rates of nicotine use may be higher than general population
  - *Ehret et al 2007*: 40% compared to 26.5%
- Other drug use
  - No studies

40

Substance use and HD

- One study (Schultz et al.) with 1849 participants:
  - Alcohol: 1.0 years earlier than control (female: 1.3 years earlier; male: 0.9 years earlier)
  - Tobacco: 2.3 years earlier than control group (stronger effect size for females)
  - Drugs: 3.3 years earlier than control (female: 4.6 years earlier, male: 2.5 years earlier)
  - Proposed mechanisms: increased dopamine activity via substance abuse (cocaine/amphetamines>nicotine>alcohol)
  - Conclusion: Given the substantial effect size (particularly for women), interventions in SUD could reduce HD age of motor onset

41

TM

- Chorea progression
- Executive function decline

- Recently started a relationship
- Distanced himself somewhat from mother and brother

- Continues to rely on EtOH to sleep
- Chronic suicidality partially improved

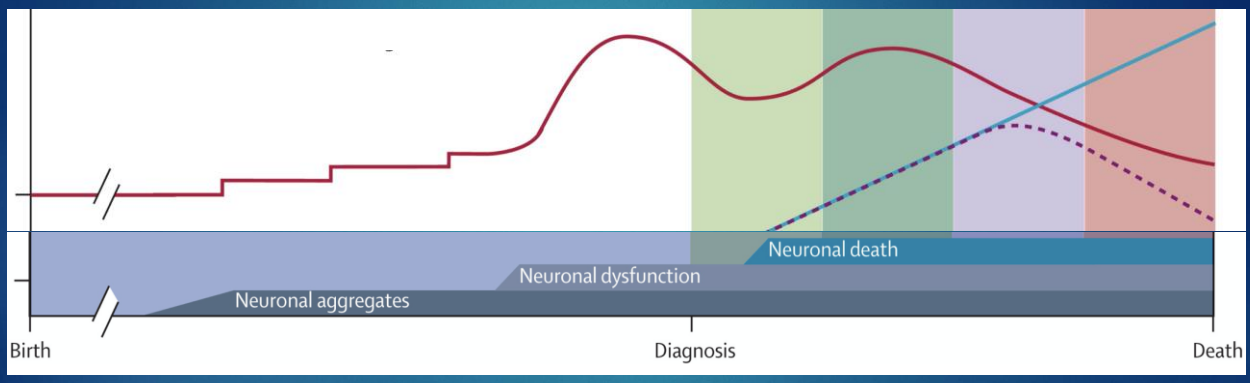
42

Suicidality

- Up to 20x more common in HD patients than the general population
- Most common around the time of diagnosis and with loss of independence
- Complicated by attention-seeking behavior ("Acquired Personality Disorder")
- Families and caregivers
  - Essential in maintaining safety and formulating a safety plan
  - Educate about indications for inpatient hospitalization before it is needed
- Cognitive issues
  - Impulsivity leads to increased risk
  - Memory decline may mitigate or increase risk

43

Suicidal ideation



44

Watch out for…

- New aggression – depression, cognitive decline, physical illness, pain
- Impulsivity – cognitive decline
- Increased need for attention – depression, anxiety, cognitive decline
- Hallucinations or delusions – physical illness, pain, medication side effect

- Social withdrawal – depression, anxiety, cognitive decline
- Irritability -- depression, cognitive decline, physical illness, pain, medication side effect

45

Psychopharmacology in HD

46

- Very little evidence of efficacy of psychiatric medications in this population
- Few studies, poorly done
  - Much of the time we are treating symptoms that are a direct result of HD subcortical degeneration
    - Apathy
    - Impulsivity
    - Perseveration
    - Amotivation

46

Psychopharmacology in HD

47

- Guiding principles:
  - Treat diagnosable psychiatric illness as you would with any patient
  - High potency typical antipsychotics for movement disorder and impulsivity/agitation
  - High potency typical antipsychotics for those unable to tolerate VMAT inhibitors or for whom they are contraindicated
  - SSRIs for perseveration, hypersexuality
  - Avoid benzodiazepines, stimulants when possible
  - It may take several medication trials to optimize treatment
  - Much of management will be behavioral

47

Behavioral interventions

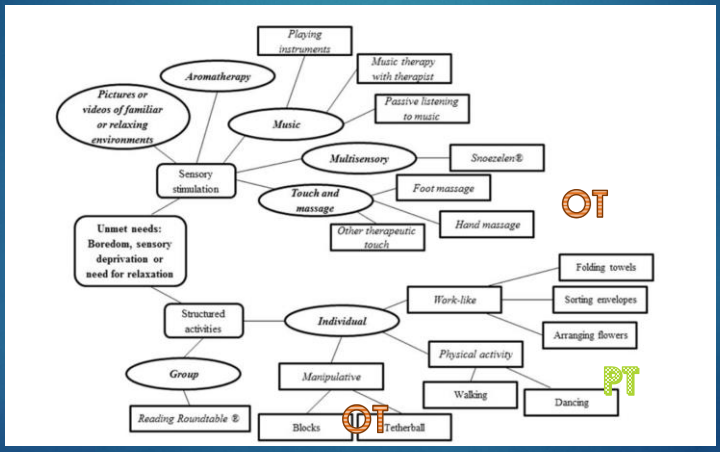
- Collaboration with PT/OT/SLP/nutrition!
- Interventions can be based on symptoms (aggression, anxiety, ...) or based on hypothesized cause of symptoms
  - Unmet needs
  - Presence of environmental irritants
- When a person can express their thoughts/feelings, we often treat based on a combination of these
- More complicated with more severe cognitive issues or lack of awareness of the link between cause and symptom

48

Behavioral/environmental interventions

Family/Caregivers

Other therapists



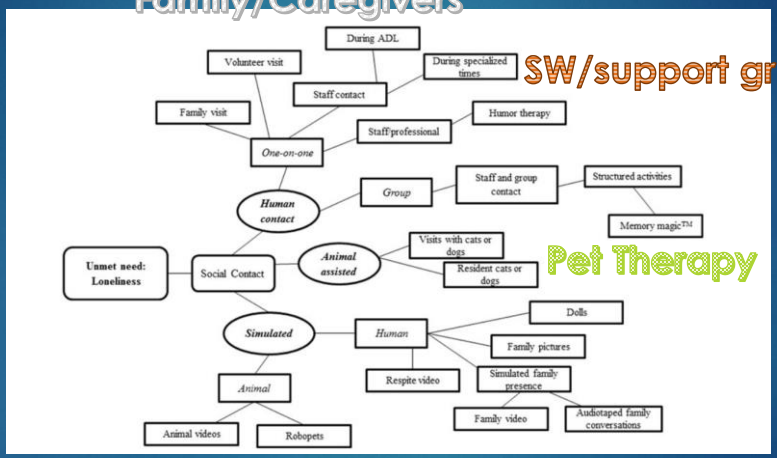
49

Behavioral/environmental interventions

Family/Caregivers

SW/support groups

Pet Therapy



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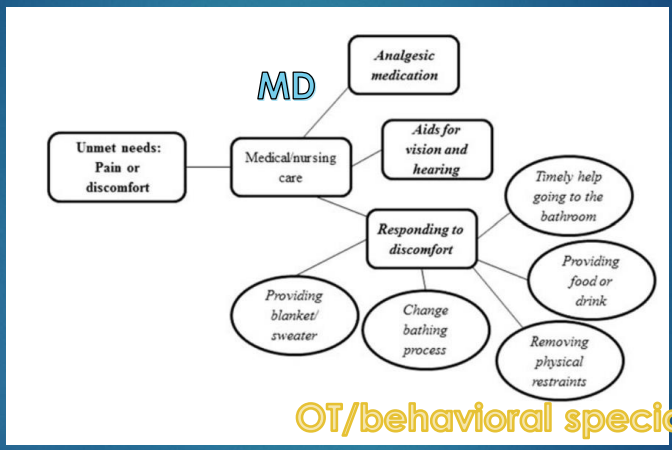
Behavioral/environmental interventions



51

AG

- 63 year-old woman with HD diagnosis 9 years ago when family noticed she was "clumsy"
- Gradual decline in physical functioning over time with recent trouble swallowing, needing the Heimlich maneuver frequently
- More impulsive and perseverative
- Frequently frustrated and hits family and paid caregivers when she does not "get her way."
- 20 lb weight loss over several months; does not sit still to eat
- Family petitions 302 for inability to care, aggression

52

AG

- Noted to be pleasant and cooperative on the psychiatric unit
- Difficult to redirect off certain benign subjects when family visits
- Noted to be eating a lot of food quickly

- Medications changed to help with mealtimes
  - Olanzapine qam and hs for impulsivity, chorea
  - Quetiapine 30 min before meals
- Doing better at home with less aggression
- Gained weight back
- Family looking into skilled nursing placement vs respite care

53

Nutrition

- HD increases metabolism
  - Movements
  - General need for more energy, up to 5000 cal/day
- Feeding
  - Swallow is affected by HD
    - Coordination
    - Tongue movements
  - Impulsivity
    - Teach patients to slow down

54

Inpatient Psychiatric Care

55

- Last resort when psychiatric illness or behavioral problems cannot be managed outpatient
- Close collaboration of the HD team with the inpatient psychiatry team helps optimize treatment

55

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56