TRINITY COLLEGE DUBLIN

Huntington's disease A Neuropsychiatry Perspective Part II

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HDANI
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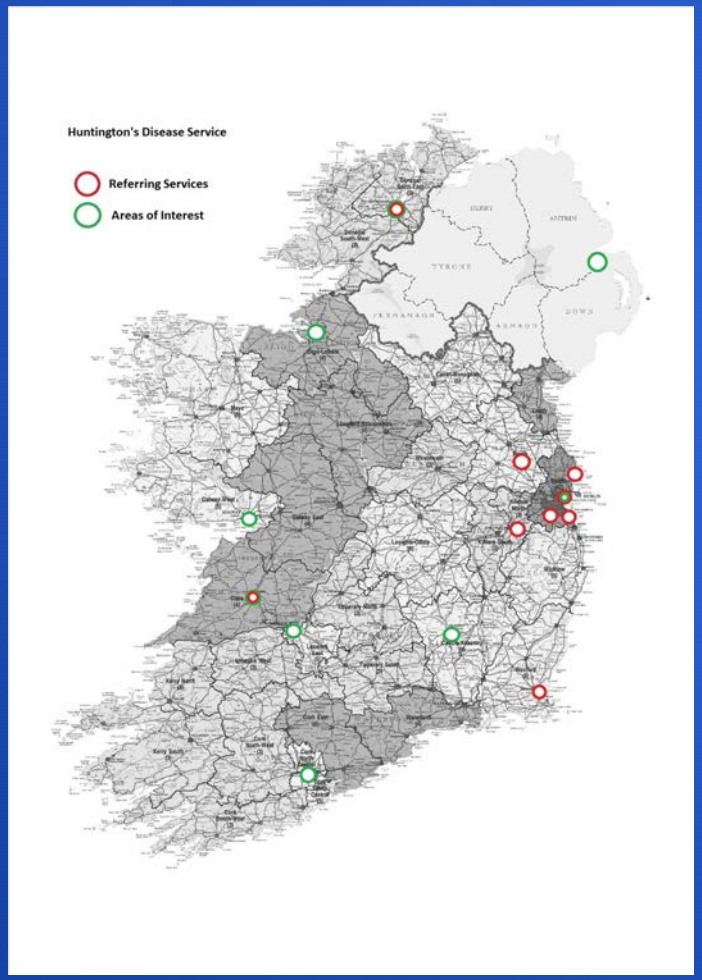
Objectives

- Introduction and Background
- Understanding HD
- Genetics
- Clinical presentations
- Medication Management
- Future directions

Bloomfield Health Services Rathfarnham

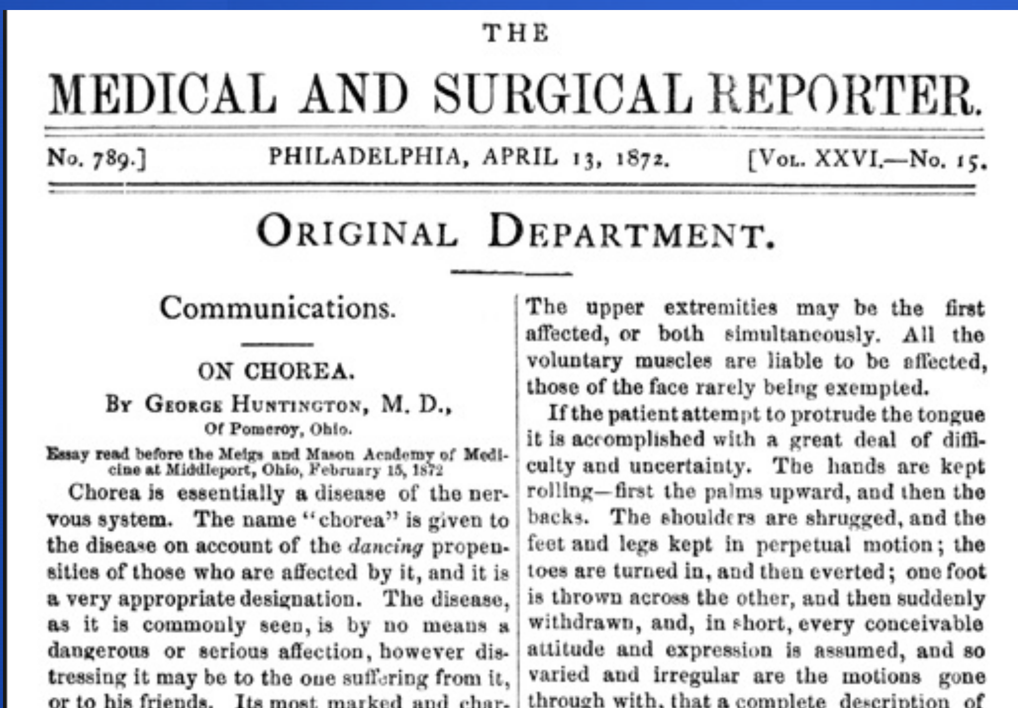


- 200 year old not for profit Charity based on the Quaker ethos and principles
- 150 beds including 36 bed Nursing home and 114 beds in the Approved Center
- Academic affiliations with TCD, UCD, UL and UCC
- Units for adult male and female residents
- Full MDT service: Psychiatry, Medicine, Psychology, Pharmacy, Physiotherapy, Social Work, Occupational therapy, Nursing Staff, Nutrition, Optician, Chiropodist and access to SALT and Palliative Medicine

Ongoing HD Service Developments

- Developing Care Programmes with MDT 1-2 per year.. Detect problems… follow up may help familiarize individuals and families with services
- Day services (Increase time to long term care) would like to offer respite in the future
- Mental Health Wellness Clinic and support for those recently diagnosed
- Clinical placements for students
- Educational programs and support services for health care professionals caring for those with HD
- Explore best practices in Europe .. And around the Globe
- Research …. Participation in research.. A more adaptive coping strategy.. Hope is vital

Huntington's disease (HD)



THE

MEDICAL AND SURGICAL REPORTER.

No. 789.] PHILADELPHIA, APRIL 13, 1872. [Vol. XXVI.—No. 15.

ORIGINAL DEPARTMENT.

Communications.

ON CHOREA.

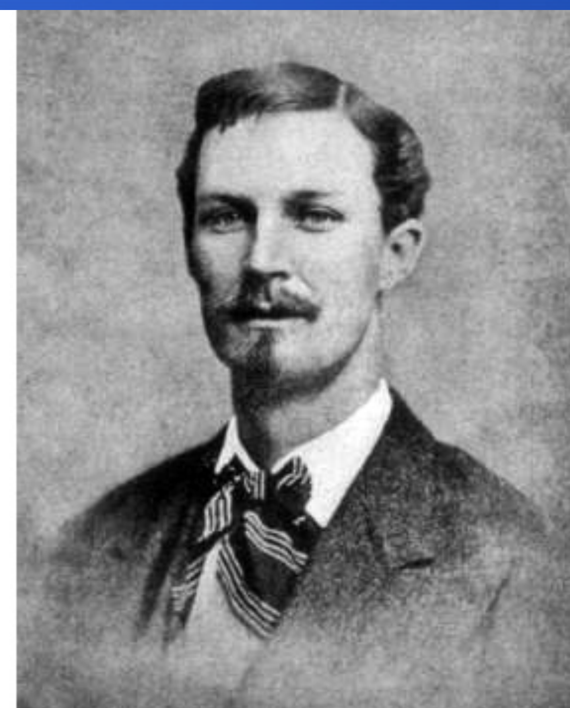
By George Huntington, M. D.,
Of Pomeroy, Ohio.

Essay read before the Meigs and Mason Academy of Medicine at Middleport, Ohio, February 15, 1872

Chorea is essentially a disease of the nervous system. The name "chorea" is given to the disease on account of the *dancing* propensities of those who are affected by it, and it is a very appropriate designation. The disease, as it is commonly seen, is by no means a dangerous or serious affection, however distressing it may be to the one suffering from it, or to his friends. Its most marked and char-

The upper extremities may be the first affected, or both simultaneously. All the voluntary muscles are liable to be affected, those of the face rarely being exempted.

If the patient attempt to protrude the tongue it is accomplished with a great deal of difficulty and uncertainty. The hands are kept rolling—first the palms upward, and then the backs. The shoulders are shrugged, and the feet and legs kept in perpetual motion; the toes are turned in, and then everted; one foot is thrown across the other, and then suddenly withdrawn, and, in short, every conceivable attitude and expression is assumed, and so varied and irregular are the motions gone through with, that a complete description of



Epidemiology of HD

- Estimated 750 individuals in Ireland with HD and 1,500 may be at risk
- UK approximately 3,600 affected
- Worldwide 10.6-13.7 per 100,000 have the disease
- US and Northern Europe and Australia is 5.7 per 100,000 and much lower prevalence of 0.40 per 100,000 in Asia
- Rare in Finland and Japan: large cohorts in Scotland and Venezuela
- Sporadic in 5-8% of diagnosed patients
- HD present all populations

Genetics

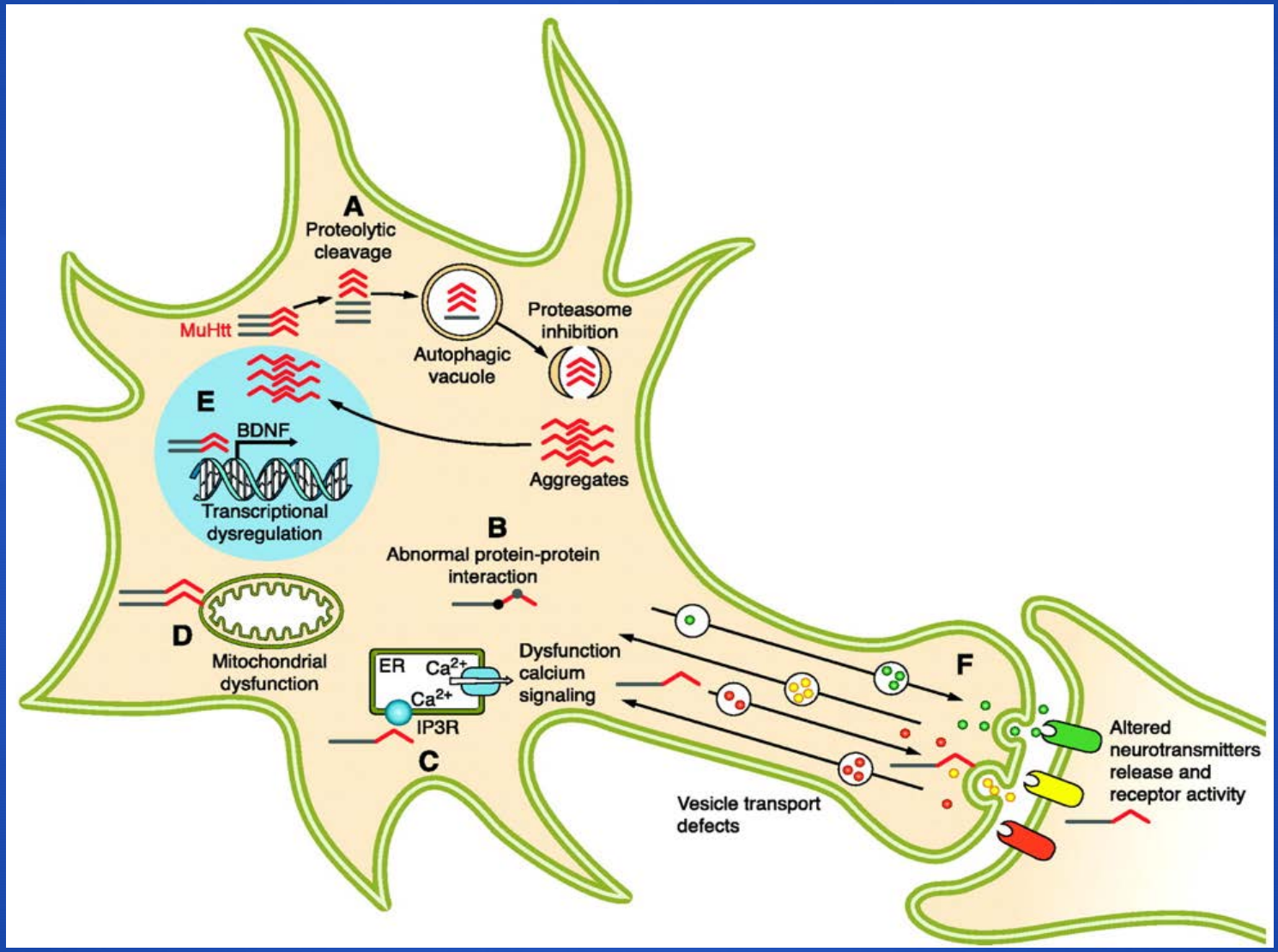
- Autosomal Dominant (AD) means if 1 parent has the gene then each child has 50% chance of inheriting it, males and females are at equal risk
- Delayed onset ..most present in 4^{th} and 5^{th} decade, 10% after aged 60 age of onset
- 10% onset before aged 20 (Juvenile HD): Bradykinesia, dystonia and rigidity as opposed to chorea. Individuals with Westphal variant HD have more hypokinetic features

Genetic Counseling

- Testing to confirm dx, predictive presymptomatic or prenatal testing… Only 5-25% of those at risk go for testing (Morrison, 2014).. Stigma
- Also pre-implantation genetic counseling available in some countries during IVF treatment
- CAG repeats: 27-35 is the upper limit of "normal" intermediate alleles: 30-35 grey zone
- 2-5% cases no known fhx

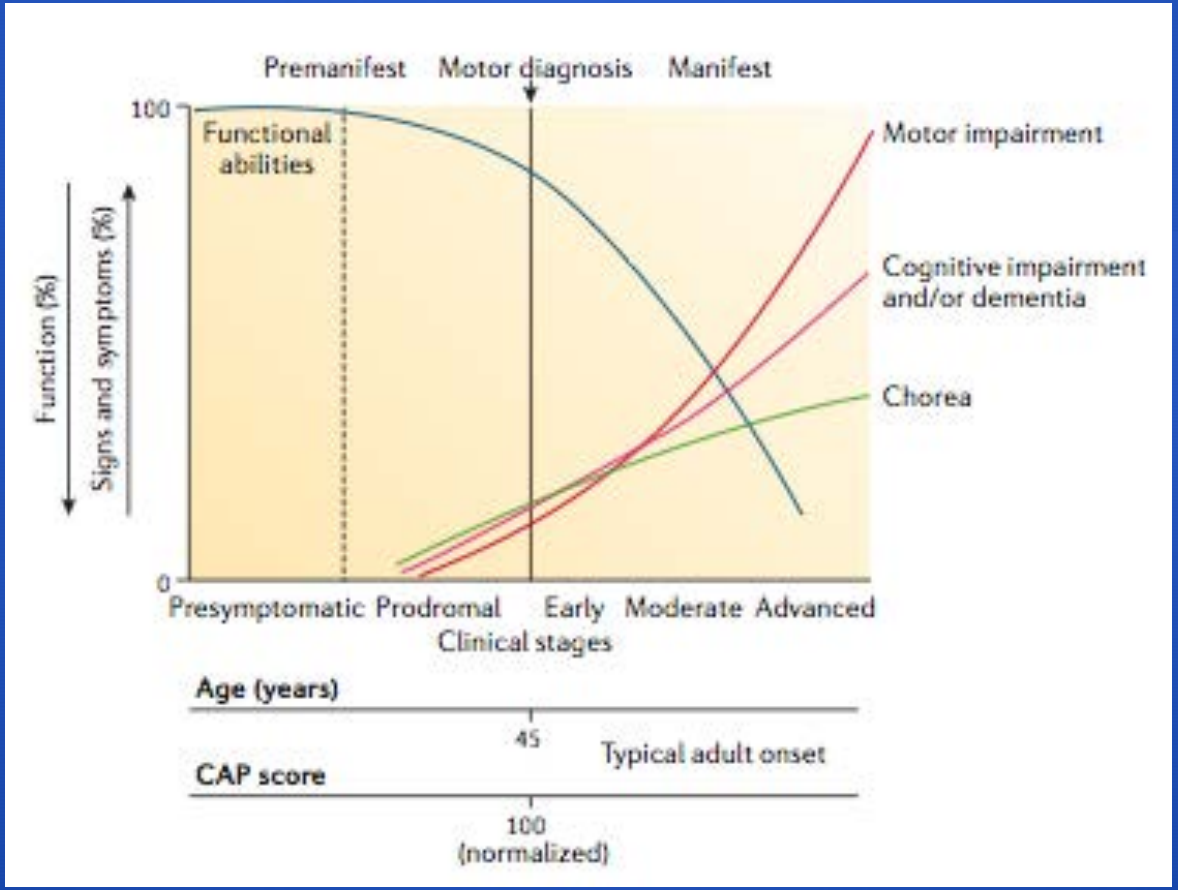
Function of Huntingtin Protein?

- Normal Huntingtin protein has 10-35 glutamines
- Plays a critical role in cell function
- Interacts with proteins found only in the brain
- In HD, the proteins do not fold into functional proteins; they tangle into insoluble aggregates (lumps) which then interfere with nerve cell function
- Accumulation of abnormal protein leads to neuronal cell death – exact mechanism unclear as yet



Key Cellular Pathogenic Mechanisms implicated in HD (Zuccatto et al, 2010)

Natural History (Ross et al, 2014)



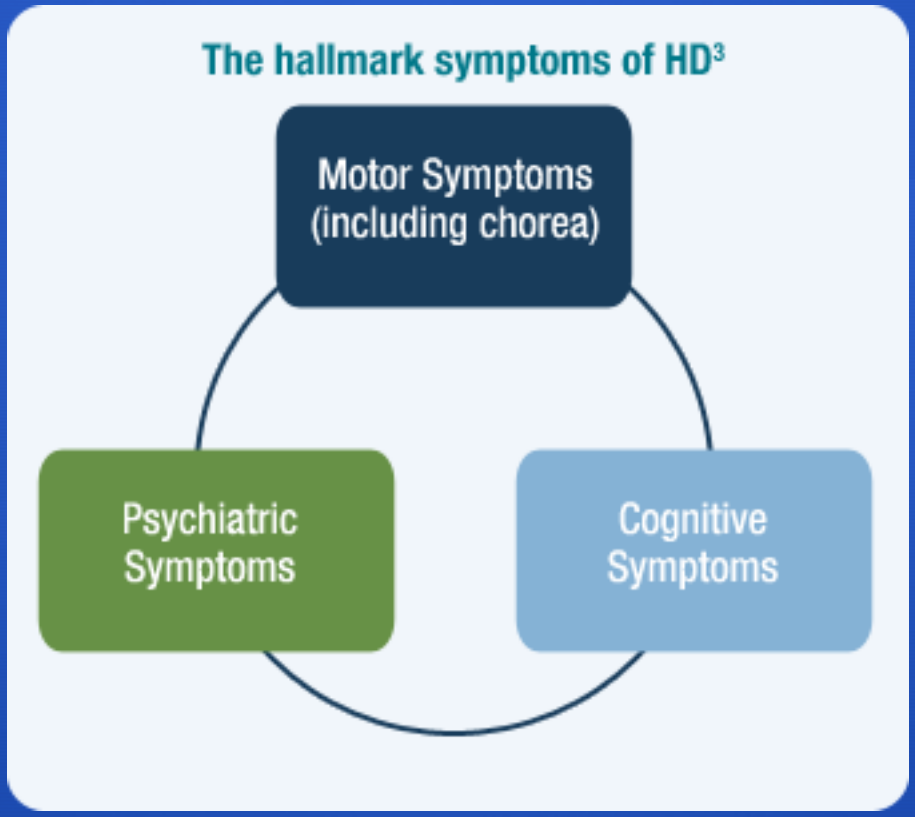
Diagnosis

- Clinical diagnosis: Self reported symptoms include cognitive/ emotional difficulties and difficulties sleeping
- Early subtle motor signs, verbal memory and smell as early possible manifestations
- 24-79% of individuals may have psychiatric signs before diagnosis, may develop impaired thinking (cognitive) function
- Unexplained characteristic movement disorder . Family History may be missing
- Confirmed by gene test

Juvenile HD

- Chorea less prominent a feature
- Presenting symptoms may include: attention deficits, behavioural disorders, school failure, dystonia, bradykinesia and sometimes tremor
- Seizures may occur (rare in adults)
- Maybe associated with paternal transmission

Clinical Features



Case Study 1

- Ms Q 28 year old female with HD, history of substance abuse, self harm and psychosis referred from Psychiatry services with poor self care and low levels of motivation
- Father recently died from HD
- Poor appetite (BMI 18), rigid behaviors, isolation, apathy, verbal aggression and threats of violence, poor self care and obvious chorea and responding to internal stimuli (Psychosis)
- Treatment plan: supportive, education, behavioral program (reinforcing desired behaviors with positive reinforcements), weekly weights, medication changes (antidepressant and anti psychotics) nutritional supplements and psychological support nb bereavement

Case Study continued

- OT, SALT, Psychology, Social Work, Chaplin, Physiotherapy, Exercise Assistant, Dietician, Dental, Pharmacist, GP, Nursing and Psychiatry - regular MDT meetings weekly. Neurology OPD.
- Support to family members ongoing
- Slowly less isolated, eating now in pantry (BMI 19.6), going out to movies, for pizza, increased attention to hygiene, participating in some ward activities, beginning to enjoy visits with her family, tolerating meds no adverse effects (reported apart from hyper salivation)
- Advanced care directives to be explored: Still declining national screenings: remains a falls risk due to chorea but her quality of life is slowly improving

Cognitive Function

Cognitive Symptoms

- May present initially as a loss of speed and mental flexibility during complex tasks
- Changes in executive function rather than learning and memory: difficulties with sequencing, organizing and prioritizing information
- Cognitive and behavioural changes may precede the motor symptoms
- May be referred to as neurocognitive disorder
- Modafanil increased alertness: no other meds have been reported to improve cognition e.g. acetylcholinesterase inhibitors (Cubo, 2006) – donepezil, galantamine or rivastigmine

Cognitive and Behavioral Symptoms

- Subcortical syndrome
- Executive function impairment
- Learning and memory
- Processing speed
- Spatial perception
- Denial anosognosia "unawareness"
- Disorganization
- Lack of Initiation may be apathy
- Perseveration
- Impulsivity
- Irritability

Obstacles for those with HD

- Loss of Job
- Loss of independence
- Changes in social life
- Difficulties with mobility
- Lack of understanding and tolerance
- Difficulties with emotional control

Behavioral difficulties

- Drive and initiative (frontal connections) try joint participation
- Mental Flexibility – familiar fixed routines
- One thing at a time
- Difficulties with quality of performance
- Hygiene and self care

Behavioral problems

- Disinhibition
- Sympathy and empathy – not under their control
- Depression
- Irritability and Aggression
- Denial of illness
- Not inevitable with disease progression

Symptomatic Treatments

- Lack of definitive treatments
- Antipsychotics for chorea but may exacerbate dystonia and bradykinesia later in disease. Also may exacerbate impaired cognition causing delirium
- Reevaluate meds regularly… d/c unnecessary meds .. Avoid polypharmacy
- Symptoms may vary between family members

Treatments

- Individuals with HD are highly sensitive to medication side effects
- Education, support and environmental management are vital
- Caregiver information crucial but remember to speak to both alone as some area may be difficult to talk about – sexual function, driving or irritability
- Explore patients interest in alternative and experimental treatments - always tell Team about OTC meds!

Motor Symptoms

Motor Symptoms

- Impairment of voluntary movements reducing manual dexterity, eye movements, affecting speech, swallowing, balance (causing falls).
- As disorder progresses chorea lessens and rigidity, bradykinesia and dystonia develop
- Meds may worsen other aspects of movement disorder, cognition or mood

Treatment of Motor Symptoms

- Decide if treatment needed? Interfering with activities or daily living (ADL's)?
- Are falls causing accidents or falls? Ataxia? Meds may help gross motor control
- Consider non pharmacological interventions .. Treat stress, anxiety or depression .. Calm predictable environment
- Assistive devices can be helpful: Physiotherapy and OT referral
- Realistic expectations .. Meds will not stop illness and s/e may worsen risk of falls (sedation or rigidity) and impair speech

Meds for Chorea (Rosenblatt et al, 2010)

Class	Medications	Starting PO dose	Max Daily Dose	Adverse effects
Antipsychotics	Olanzapine	2.5 mgs nocte	20 mgs	Metabolic effects, sedation, Parkinsonism, wt gain
	Risperidone	0.5 – 1 mgs daily	6 mgs	As above less appetite
	Quetiapine	25 mgs daily	750 mgs	As above less effects on lipids and glucose
	Sulpride	50-100 mgs	2400 mgs	Agitation, dystonia, akathisia, sedation, low bp, dry mouth, constipation
	Haloperidol Tiapride	0.5 – 1 mgs 200 mgs	6-8 mgs 1200 mgs	EPSE, low bp, anticholinergic Fatigue
Benzodiazepines	Clonazepam	0.5 mgs	4 mgs	Sedation, ataxia, apathy, cognitive impair, wd seizures
	Diazepam	1.25mgs	20 mgs	As above
Dopamine depleting agents	Tetrabenazine	12.5 mgs (go slow)	200 mgs	Depression and sedation

Treatment of Motor Symptoms

- 2008 FDA approved tetrabenazine for motor symptoms. Side effects :hypotension, sedation/somnolence, fatigue, insomnia, depression, suicide, anxiety, restlessness and apathy
- First HD and ARC HD (Auspex and Teva) Phase 3 trial of SD-809 Deutetrabenzine a novel VMAT2 Inhibitor, FDA new drug application 2016. Weight gain reported , S/E like placebo
- Tiapride: D2 antagonist available in Europe
- Benzos can be used for chorea but sedation and cognitive effects limit their use
- Antipsychotics such as olanzapine, risperidone or quetiapine may be tried

Rigidity, spasticity and dystonia

- Clonazepam or baclofen (Bradykinesia may increase)
- Tizanidine can help spasticity
- Antiparkinson's meds such as amantadine or levodopa/ carbidopa may cause delirium
- Physiotherapy to help prevent contractures
- Botox may help if a small group of muscle is rigid

Psychiatric Symptoms

Psychiatric Symptoms

- Symptomatic treatments have improved.. Need to optimize.. Develop guidelines .. EHDN ones in development 2017
- Barriers to care include lack of insight, denial and apathy
- Behavioral symptoms can be more distressing than motor and greater impact Quality of Life (Read et al, 2013)
- Symptoms can occur at any stage but hard to recognize and treat late in disease
- Model of UK Care Programmes with MDT 1-2 per year.. Detect problems….Risk of suicide, follow up may help familiarize individuals with service

Psychiatric Symptoms

- Often under diagnosed and under treated….
- May have MDE, BAD or OCD as in general population: depression (may present as anxiety, insomnia or pain)
- Use diagnostic criteria to differentiate depression from bereavement, demoralization and from symptoms of HD itself
- Also less defined changes in mood and personality e.g. apathy, irritability or disinhibition
- Check for hypothyroid, cva, meds and alcohol
- 25% of individuals with HD attempt suicide and it is the cause of death in 8-9% of patients

Anxiety

- Anxiety symptoms common in HD but not a formal disorder
- Assess if anxiety is a symptom of depression, OCD or cognitive disorder
- Panic disorder is uncommon
- Rule out any medical conditions that be contributing: pain or sub abuse
- Decrease complexity of the environment, try to identify triggers
- Establish a predictable routine
- Sleep hygiene, exercise and light therapy to target insomnia
- Psychotherapy, relaxation therapy

OCD

- True OCD rare in HD, not as prevalent as other BG diseases e.g. Tourette syndrome… maybe familial
- May have obsessive preoccupation with certain ideas germs or contamination, checking switches or locks
- Preoccupied with past episode of being wronged, with a perceived need for something e.g object or food
- SSRIs have superseded clomipramine. May need higher doses than depression. Cognitive Behavior Therapy consider cognition
- May need antipsychotic if severe

Anxiety Treatment

- Cross titrate benzodiazepine* and antidepressant
- Review after 2-4 weeks if working adequately maintain
- If not working consider switch to alternative agent or augmentation
- Hypnotics may include zopiclone, zolpidem or trazadone – use on a short term basis ideally

Depression

- Use diagnostic criteria to differentiate depression from demoralization, transient mood states or symptoms of HD. Prevalence of 38% (Folstein 1983)
- Higher rates reported up to 69% in gene carriers (van Duijn et al, 2007)
- Psychosocial and biological factors
- May have delusions or hallucinations
- Psychomotor retardation - may appear catatonic/frozen
- R/O potential medical/neurological causes and alcohol/sub abuse
- Sensitive to s/e start low dose meds
- Always ask re suicidal thoughts

Depression Meds

Class	Medications	Start dose	Max daily dose	Adverse effects
SSRIs	Fluoxetine	10-20 mgs	60-80 mgs	Insomnia, GI, restless, wt loss
	Sertraline	25-50 mgs	200 mgs	Similar
	Citalopram	10 mgs	20 mgs	Similar
	Paroxetine	10-20 mgs	40-60 mgs	More sedation
TCAs	Nortriptyline	10-25 mgs	150-200 mgs	Antichol, TC, hypoBP and sedation
Other	Buproprion	100-200 mgs	300- 450 mgs	Seizures, agitation, dry mouth, insomnia, nausea
	Venlafaxine (XR)	25-37.5 mgs	225 mgs	HTN, Nausea, HA, constipation

Mania

- Small number develop mania: irritable, overactive decreased sleep, grandiose and impulsive. Reported that 4.8% develop Mania (Mendez, 1994)
- Poor lithium response … Unclear why?
- Sodium valproate (Epilim)
- Carbamazepine monitor for sedation, dizzy, ataxia, rash, bone marrow suppression
- Monitor bloods, care with potential pregnancy..
- May also need antipsychotic, benzo or ECT

Insomnia

- Sleep history
- Co-morbid conditions?
- Minimize day time sedation
- Education and sleep hygiene
- Least risk medication: sedating antidepressant (mirtazepine or trazodone). AP if needed e.g quetiapine or olanzapine
- Avoid benzos in ambulatory individuals
- Consider melatonin (5-10 mgs a few hours before bed per ASSM)

Agitation

- Environmental triggers or antecedents that trigger the agitation e.g. unmet needs, perceived threats
- R/o delirium if rapid onset
- Education try to avoid triggers, quiet environment and verbal de-escalation with respectful redirection, positive expression of concern etc.
- Treat co-morbid neuropsychiatric symptoms: mood, anxiety or psychosis

Agitation

- If acute and not responsive to behavioral approach may need to try meds e.g. benzo, ssri or antipsychotic
- Most behavioral and psychological symptoms improve within approximately 6- 12 weeks
- If chronic symptoms consider trial of an antipsychotic, mood stabilizer or trial of propranolol (Groves et al, 2011)
- Always consider pain as cause

Causes of pain or discomfort

- Arthritis
- Constipation, diahorrhea or reflux
- Urinary tract infection (UTI) or yeast infections
- Skin ulcers
- Tinea or podiatry concerns
- Poor vision, hearing loss or dental problems
- Headaches or muscle aches
- Diuretics at night, rebound effects from Benzos or a paradoxical reaction

Delirium

- Individuals with late stage HD particularly vulnerable
- May be hyperactive or hypoactive in presentation
- Common causes include: meds , alcohol, illicit drugs, dehydration, respiratory and utis. Check OTC meds. H/o falls look for subdural hematomas
- Consider delirium with acute behavioural change
- Treat cause and treat with environmental cues and low dose antipsychotics

Antipsychotics potential side effects

- Sedation
- Parkinsonism , EPSE's associated with cognitive impairment and ↓ ADL's (Larson, 1987 and Tinetti, 1988) and Tardive Dyskinesia
- Increased risk of infection or Neuroleptic Malignant Syndrome
- Increased risk of falls and fractures
- Increased risk of blood clots
- Increased risk of stroke or sudden death
- May worsen cognition or other dementia symptoms

SCZ and SCZ like disorders

- Less common in HD than mood disorders
- R/o delirium, drug intoxication/withdrawal
- Treat with antipsychotics at higher doses than needed for chorea
- Advise caregivers to avoid confrontation

Apathy

- It is a core feature that increases over time
- Consider levels of motivation, initiative, interests and emotion
- Try to rule out inability to perform motor or cognitive tasks
- r/o depression or co-existing medical co-morbidity
- Scheduling and prompting
- Trial of antidepressant if depressed
- Consider activating antidepressant or careful trial of stimulant

In Development ….

Biomarkers

Something you can measure:

1. Fluids: CSF, blood, saliva, gene expression, metabolomics
2. Imaging: MRI, MS and perhaps PET with specific ligands
3. Electrophysiological: EEG, EMG
4. Physiological: Qmotor, strength testing, eye tracking

Gene therapy

- Strategies to reduce the amount of mutated protein ..
- Interfere with DNA to mRNA process post transcription
- Design a molecule that can identify and breakdown the mRNA carrying instructions for a specific protein.. Censoring the message…. Silencing the gene coding for muHtt ..
- Target mutHTT with binding intrabodies (e.g. Happ1 and EM48) leading to a complex marked for "garbage disposal"

Environmental modifiers

- Mouse models demonstrated that enriched environments delays onset of symptoms
- Perhaps presymptomatic lifestyle may affects age of onset in humans
- Age of onset Alzheimer's Disease and Parkinson's Disease can be influenced by type and level of activity undertaken prior to development of symptoms
- Avoid a passive lifestyle leisure ..
- Rehabilitation program improved gait, balance, self confidence and social outcomes (Frich et al, 2014)

Surgical Approaches

- Cell replacement Stem cell…neuroprotection with delivery of neurotrophic factors, immune modulation and can transplanted cells grow into correct neurons and re-wire?
- Deep brain stimulation – used in depression, OCD, Epilepsy and HD (Jan Vesper Germany) stimulate Globus pallidus internal and external, significant improvement in Chorea reported

Why have hope?

- Primary Cause of HD is known – accurate diagnosis
- Targets for Interventions have been identified
- A predictive test is available – identify presymptomatic individuals
- Intense scientific activity – insights for other neurodegenerative diseases including stem cells, gene therapy and informatics
- There is an active organized receptive HD community

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THANK YOU FOR LISTENING!

Questions?