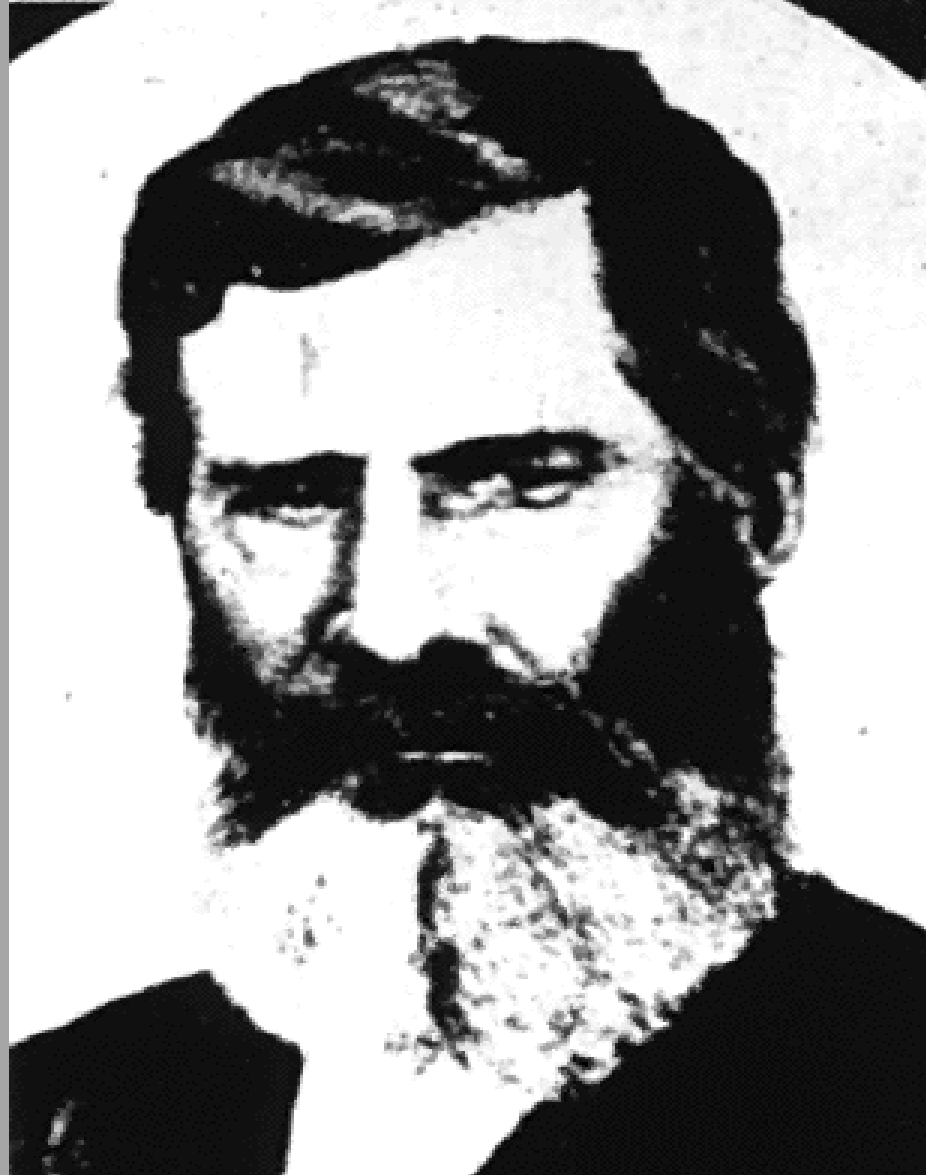


HUNTINGTON DISEASE: PATHOGENESIS, SYMPTOMS, AND TREATMENTS

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The man



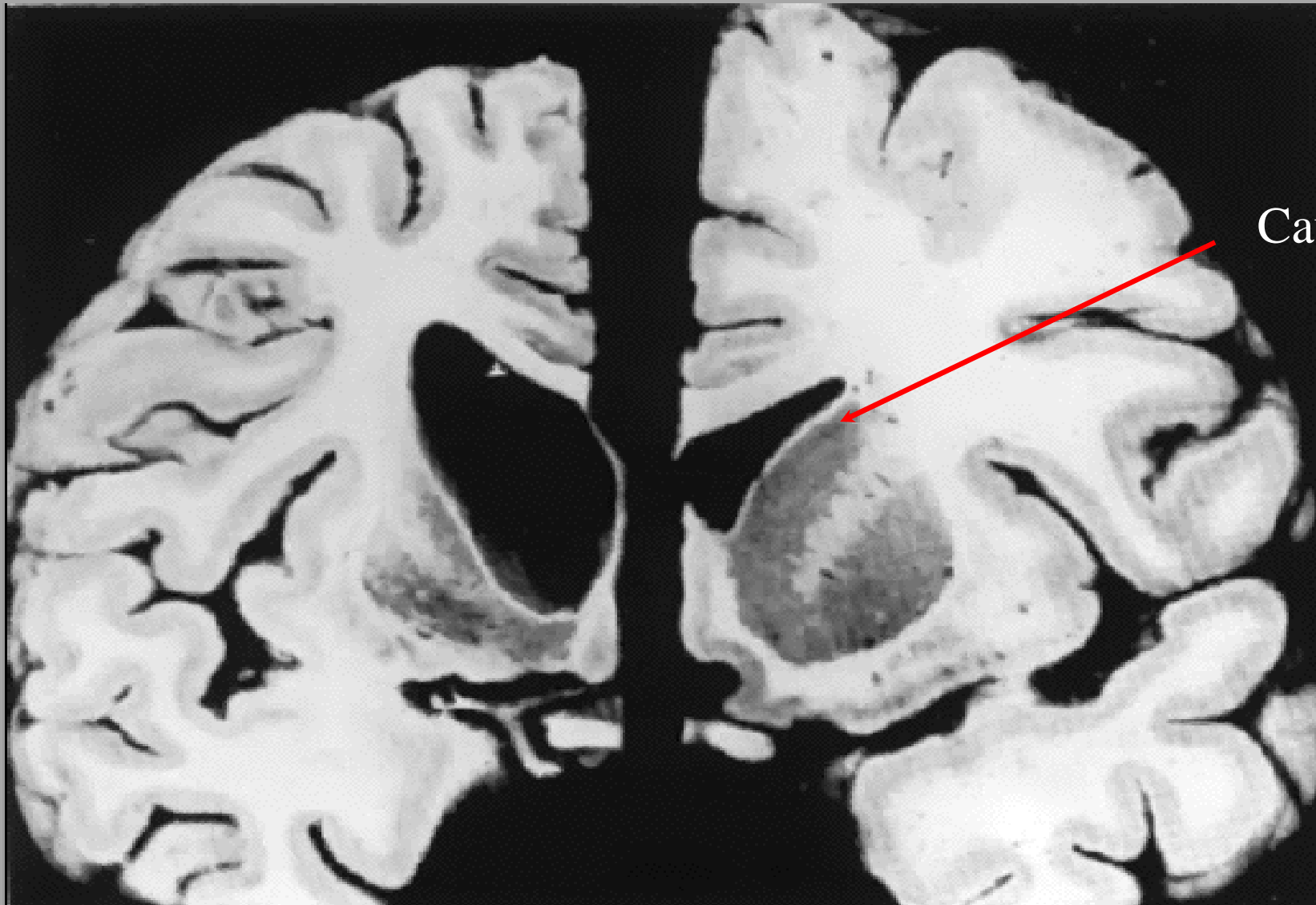
Huntington Disease

- ☼ Symptoms (which can vary between HD patients):
 - ☼ Movements – chorea, may appear fidgety at first
 - ☼ Cognition – Problems with short term memory, ability to perform daily tasks
 - ☼ Behavior – Emotion, personality, affect changes, mood swings, easily irritated
- ☼ Age of onset varies – avg age 35-40, but can range from childhood to over 80 years
- ☼ Course of disease 10-20 years
- ☼ Autosomal dominant
- ☼ 3-10/100,000

Huntington disease: Brain pathology

HD brain

Normal brain



Caudate

PATHOLOGY

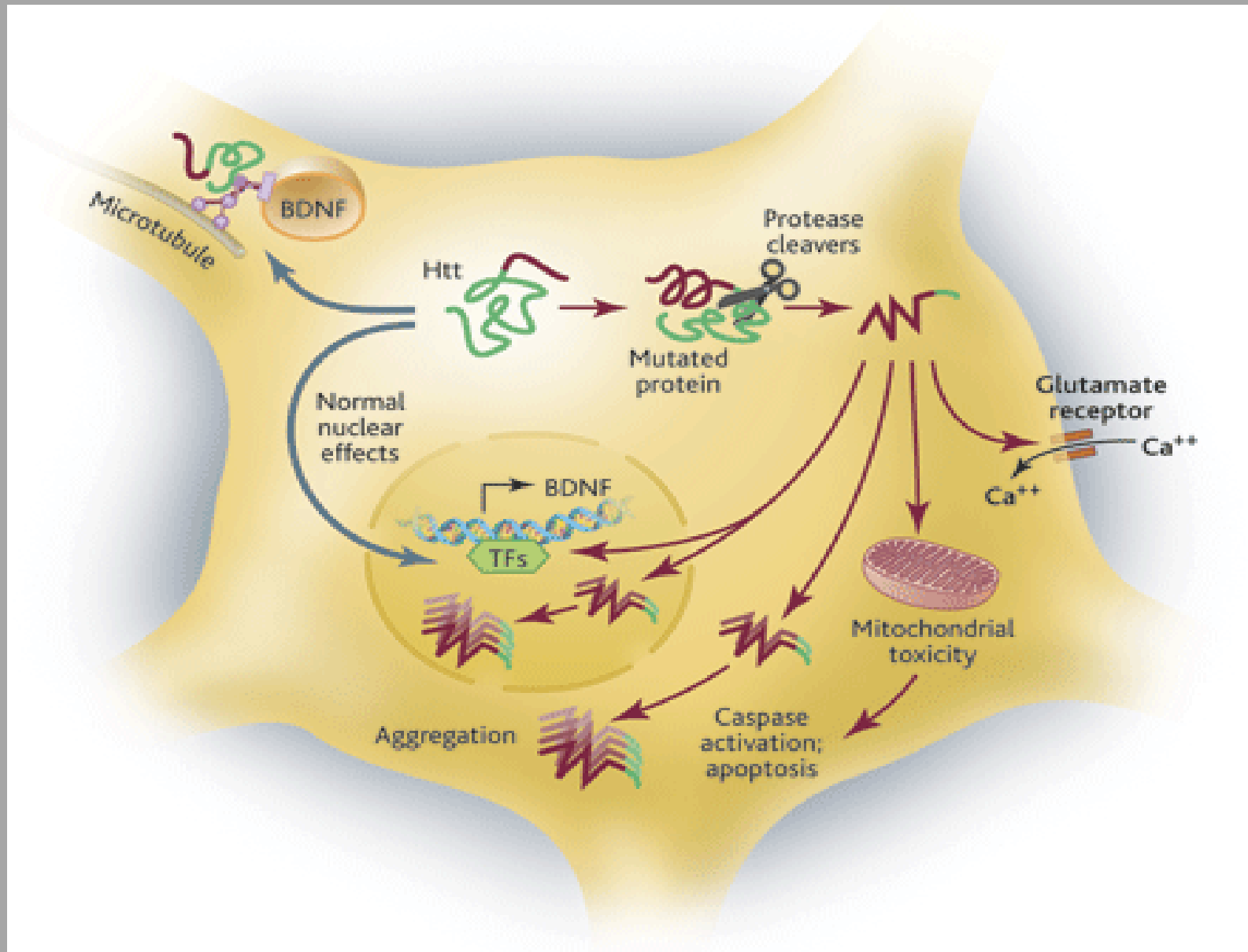
MACROSCOPIC

- atrophy of caudate
- atrophy of putamen and globus pallidus
- reduced cerebral volume
 - frontal lobes most conspicuously atrophic

MICROSCOPIC

- neuronal loss & gliosis (scarring)
 - striatum (caudate & putamen)
 - globus pallidus
 - cortex
 - thalamus (esp ventrolateral nuclei)
 - substantia nigra

Cellular pathology in HD



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MOVEMENT DISORDER

- Chorea-quick, involuntary movements
- Abnormal eye movements
 - interrupted pursuit (tracking eye movements)
 - hypometric saccades (rapid eye movements)
- tongue impersistence
- impaired rapid alternating movements
- Akathisia – inner restlessness
- late stage bradykinesia (slow movements), rigidity, spasticity, dystonia
- Dysarthria – slurred speech
- Dysphagia – trouble swallowing

Cognitive impairment in HD

EARLY, CONSPICUOUS IMPAIRMENTS

- frontal lobe impairments
 - reasoning, judgement, decision-making, planning
 - perseveration
 - attentional deficits
- Slowing (bradyphrenia)

LATER IMPAIRMENTS

- memory deficits
- other cortical functions
 - spatio-perceptual
 - language
 - Anosagnosia (lack of awareness)?

Psychiatric and behavioral problems are ...

The most significant burden on caregivers

One of the most important determinant of
care decisions

Personality Change

“Pseudodepressive”

- apathy
- withdrawal
- neglect

“Pseudopsychopathic”

- irritability
- impulsivity
- disinhibition

Psychiatric disorder in HD: prevalence

- 30 % initially present with psychiatric problems
- up to 30% misdiagnosed as psychiatric disorder
 - personality disorder and neurosis
 - mood disorder
 - schizophrenia
- overall prevalence of psychiatric disorder : 40-80%

Depression

- Major depression in 40-63% (Folstein *et al*, 1983; HSG, 2001)
- Twice prevalence of Alzheimer (Mindham *et al*, 1985)
- May precede neurological symptoms
 - ↑ prevalence in at-risk subjects regardless of genetic status (Watt & Sellar, 1993; Shiwach & Norbury, 1994)

Bipolar Affective Disorder

- Defined by occurrence of hypomania / mania
- Widely varying prevalence rates – 2-12%

Deliberate Self -Harm and Suicide

- 4 x ↑ suicide rate
- *Note*, “intention” not same as action.
- Up to 20% deliberate self-harm
- ↑ suicide rate in all risk categories
- Risk factors for suicide:-
 - having no children
 - unmarried
 - living alone
 - family history of suicide
 - no contact with others who have HD
 - earlier stages of disease

Psychosis

- 3 - 12 % life-time risk in HD
- may precede movement disorder
- diagnosis of HD often missed
- prevalence increases with disease duration
- symptomatology may resemble schizophrenia
- persistent delusional disorder in about 8%
- delusions / hallucinations increase from 2 -9% with illness progression

Obsessive Compulsive Disorder

- several case reports
- unknown prevalence
- perseveration is very common
- may contribute to management problems

Substance abuse

- No clear evidence of higher rates of misuse or dependence in HD

Assessment: special problems

- Communication difficulties
 - dysarthria
 - cognitive impairment
- Fear of hospitalization, medication
- Denial / lack of insight
- importance of informant history

Assessment of behavioral problems

- 1) Frequency, severity of behavior
- 2) Risk assessment
- 3) What is the cause ?
 - role of cognitive impairment / personality change
 - psychiatric disorder
 - Psychosis
 - Depression
 - environment
 - social factors
- 4) Informant history

Treatment: non-pharmacological

1. Explanation
 - i. Provide information about behaviour and HD
2. Support
 - i. Regular contact
 - ii. Point of contact in crises
 - iii. Social services
3. Psychological Interventions
 - i. Consistency and patience
 - ii. Behavior analysis and modification
4. Risk management
 - i. Hospitalization when necessary

Treatment: pharmacological

PRINCIPLES OF DRUG TREATMENT

1. Stop or reduce medication if possible
2. Treat psychiatric disorder
 - psychiatric drugs work best for psychiatric disorders
 - special considerations re side-effects
3. Behaviour-modifying drugs
 - limited evidence of efficacy
 - trial with careful monitoring
 - withdraw if no clear significant benefit
 - avoid harm

Treatment of Mood disorders

ANTIDEPRESSANTS

- case reports and series support efficacy
- no controlled trials or comparison studies
 - SSRI's (serotonin reuptake inhibitors) recommended
 - Prozac (fluoxetine) – increases levels of BDNF in animals
 - Zoloft (Sertraline) – increases levels of BDNF in animals

Electroconvulsive therapy

- 3 series, 9 patients:- 8 improved, 1 movement disorder

Lithium

- 1 placebo-controlled trial for “labile mood” - ineffective

Antiepileptic drugs

- no reports

Treatment of Psychosis

- very few reports
- haloperidol effective (may need higher doses than conventionally used for movement disorder) but may worsen movements in long run
- atypical neuroleptics recommended
 - Risperadol
 - olanzapine
 - amisulpiride
 - clozapine

Symptomatic treatments

- To control involuntary movements
 - Tetrabenazine: Is effective in reducing movements, finally released as Xenazine™ in US
Lundbeck Pharmaceuticals
 - www.xenazineusa.com
 - ‘Black box warning:’ Need to be aware of possible depression when taking Tetrabenazine, may increase risk of suicide
 - Some people may metabolize tetrabenazine slowly and should not receive more than 50 mg per day (should have *CYP2D6* genetic test before going over 50 mg/day)

Symptomatic treatments

- Other medications to control involuntary movements
 - Klonopin: A little helpful; habit forming
 - Haldol: Commonly used in the past but can aggravate movements in the long run
 - Keppra: recent study found some benefit in HD patients; a commonly used antiepileptic medication

Symptomatic Treatments


- Cognition/Memory
 - Aricept
 - Mementine
- Used for treatment of dementia, such as Alzheimer disease

Other therapies

- Speech/Language and swallowing therapy
- Physical/Occupational therapy
- Cognitive therapy
- Family therapy/psychological counseling
- Respite care

Best web sites to find out about HD clinical trials

H · S · G
Huntington · Study · Group



CLINICAL TRIALS & RESEARCH STUDIES IN PROGRESS

Updated: March 2006

Therapeutic Trials	At-Risk & Observational Research Studies
<ul style="list-style-type: none">● Coenzyme Q10 Pilot Study (enrollment complete)● TETRA-HD (enrollment complete)● TREND-HD● PHEND-HD (enrollment complete)● DOMINO	<ul style="list-style-type: none">● PHAROS (enrollment complete)● PREDICT-HD● COHORT

<http://www.huntington-study-group.org/>

Also <http://www.clinicaltrials.gov>

Potential HD targeted therapies

- Minocycline
- EPA
- Creatine
- Coenzyme Q10
- RNAi
- Gene therapy
- Trophic factors
- Trehalose
- ‘Stem cell’ therapy

Helpful web sites

- ghr.nlm.nih.gov/ Genetics Home reference
- www.genetests.org/profiles/huntington/index.html
Genetests review on HD (technical)
- www.hdsa.org HDSA web site
- www.huntington-study-group.org Huntington study group site
- www.clinicaltrials.gov General site for finding research studies on a disease
- www.genome.gov Genome research branch of the National Institutes of Health