

Choreas

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ETIOLOGICAL CLASSIFICATION OF CHOREA

1. Hereditary choreas

- Huntington's disease**
- benign hereditary chorea** - nonprogressive chorea in childhood.
- neuroacanthocytosis**
- other CNS "degenerations"**: olivopontocerebellar atrophy, Azorean disease, ataxia telangiectasia, tuberous sclerosis, Hallervorden-Spatz disease, dentato-rubral-pallido-luysian atrophy (DRPLA), familial calcification of basal ganglia.
- neurometabolic disorders**: Wilson's disease, Lesch-Nyhan disease, lysosomal storage disorders, amino acid disorders, Leigh's disease, porphyria.

2. Developmental & aging choreas

- physiological chorea of infancy
- cerebral palsy (anoxic, kernicterus)
- minimal cerebral dysfunction
- buccal-oral-lingual dyskinesia and edentulous orodyskinesia in elderly
- senile chorea (probably several causes)

3. Drug-induced choreas: neuroleptics (tardive dyskinesia), antiparkinsonian drugs, CNS stimulants (amphetamines), tricyclics, oral contraceptives, anticonvulsants (phenytoin, carbamazepine, ethosuximide), anticholinergics.

4. Toxin-induced choreas: alcohol intoxication / withdrawal, anoxia, CO, Mn, Hg, Tl, toluene.

5. Metabolic causes

- hyperthyroidism
- hypoparathyroidism (various types)
- pregnancy (chorea gravidarum)
- NA \uparrow ↓, Mg \downarrow , Ca \downarrow
- hypo- and hyperglycemia (latter may cause hemichorea, hemiballism)
- acquired hepatocerebral degeneration
- nutritional (e.g. beriberi, pellagra, vitamin B₁₂ deficiency in infants)

6. Infectious / immunologic causes

- Sydenham's chorea
- encephalitis lethargica
- various other infections / postinfectious encephalitides (incl. Creutzfeldt-Jakob disease)
- systemic lupus erythematosus

HUNTINGTON DISEASE (HD)

- first recognized clinically by Waters in 1842.
- comprehensive description by George Huntington in 1872.
- PREVALENCE – 4-10 per 100,000 population (in Japan rate is only 10% of this figure).

PATHOGENESIS

Autosomal dominant inheritance

- complete penetrance - homozygotes do not differ clinically from heterozygotes!
- when family history is lacking, *autopsy reports on relatives* can unearth diagnosis in genealogy.
- spontaneous mutations available!

Unstable **expansion of CAG repeats** on chromosome 4 (4p16.3)

- normal individuals have 11-34 repeats;
- HD patients have 37-121 (overexpression of normal protein).
Despite marked variability in phenotypic expression, there is *no genetic heterogeneity!*

CAG repeat is **unstable in gametes**; change in number of repeats is transmitted to next generation, sometimes with decrease in number, but more often with increase.

- esp. **unstable in sperm**; affected fathers transmit very high repeat sequence → early disease onset in offspring.
- affected **mothers** transmit only ± 3 repeats.
N.B. many more* juvenile HD cases occur when gene is inherited from father compared to mother (*ratio $\approx 10:1$) - genetic *anticipation* (progressively earlier onset of hereditary disease in successive generations).

Spontaneous mutations occur from expansion of repeats from parents who have repeat lengths of 34 to 38 units (so-called "intermediate alleles").

Trinucleotide CAG codes for **glutamine** - increase in polyglutamine causes IT15 gene overexpression - protein is termed **HUNTINGTIN**:

- tightly binds with UBIQUITIN → *intranuclear inclusions* → mitochondrial dysfunction (MR spectroscopy demonstrates ↑lactic acid, suggesting bioenergetic defect).
- HUNTINGTIN has been suggested to be potential target for *caspase 3* (protease associated with neuronal apoptosis).

HD mRNA product is found in all body tissues, but STRIATUM is preferentially affected (it is not known why pathologic gene results in abnormalities solely in brain);

- neuron loss in *caudate & putamen* correlates with longer CAG repeat length.
- *preproenkephalin medium spiny neuron* is particularly vulnerable.

PATHOLOGY

Generalized BRAIN atrophy (with neuron loss and reactive fibrillary astrocytosis):

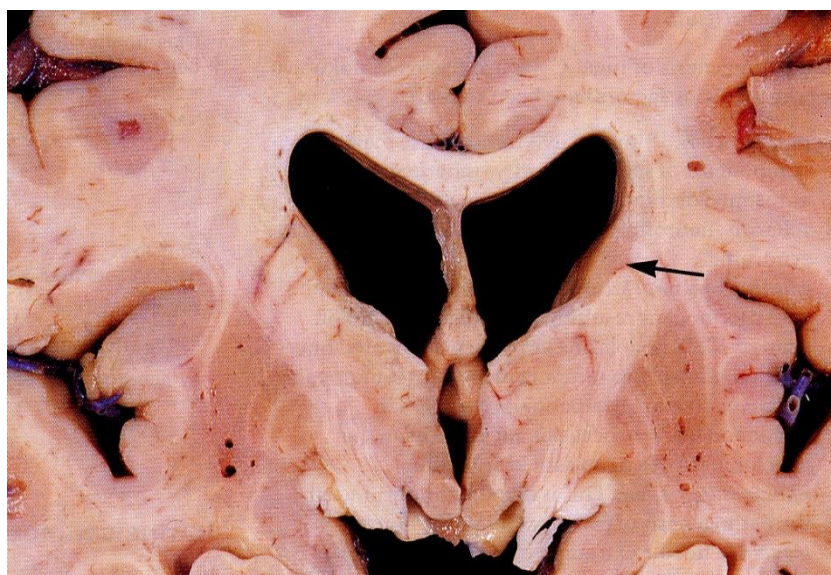
1. Neuron loss in *cortex* (especially in layer 3) - frontal lobe, less often in parietal lobe, and occasionally in entire cortex.
2. Most severe atrophy in *striatum* (particularly caudate nucleus) - severe loss of **medium spiny projection neurons** with their **GABAergic striatal efferents**.
 - *cholinergic aspiny interneurons* are preserved!
 - **marked caudate atrophy** is pathological hallmark of disease!

Affected areas contain neuronal *intranuclear inclusions** and *ubiquitin-reactive dystrophic neurites***
 **huntingtin* accumulations forming insoluble amyloid-like fibrils.
 **present only in cortex; may correlate with dementia.

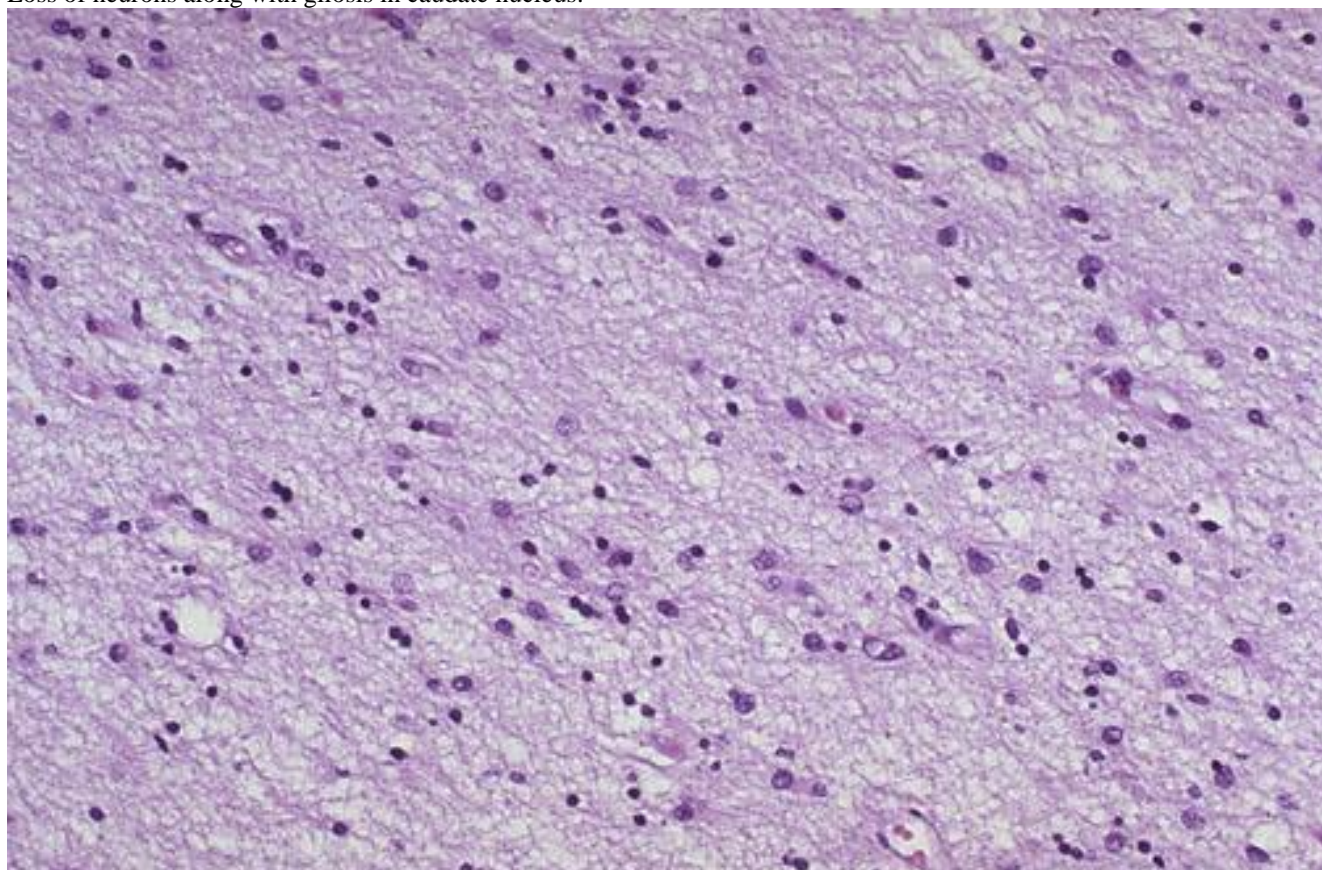
Atrophy of caudate nucleus and dilatation of lateral ventricle:



Source of picture: "WebPath - The Internet Pathology Laboratory for Medical Education" (by Edward C. Klatt, MD) >>



Loss of neurons along with gliosis in caudate nucleus:



Source of picture: "WebPath - The Internet Pathology Laboratory for Medical Education" (by Edward C. Klatt, MD) >>



PATHOPHYSIOLOGY

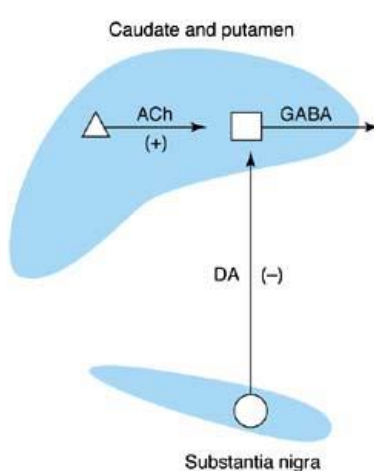
NORMA

see p. A103 >>

DA neurons *inhibit* (via D₂ receptors) and **ACh neurons** *excite* GABAergic output from striatum:

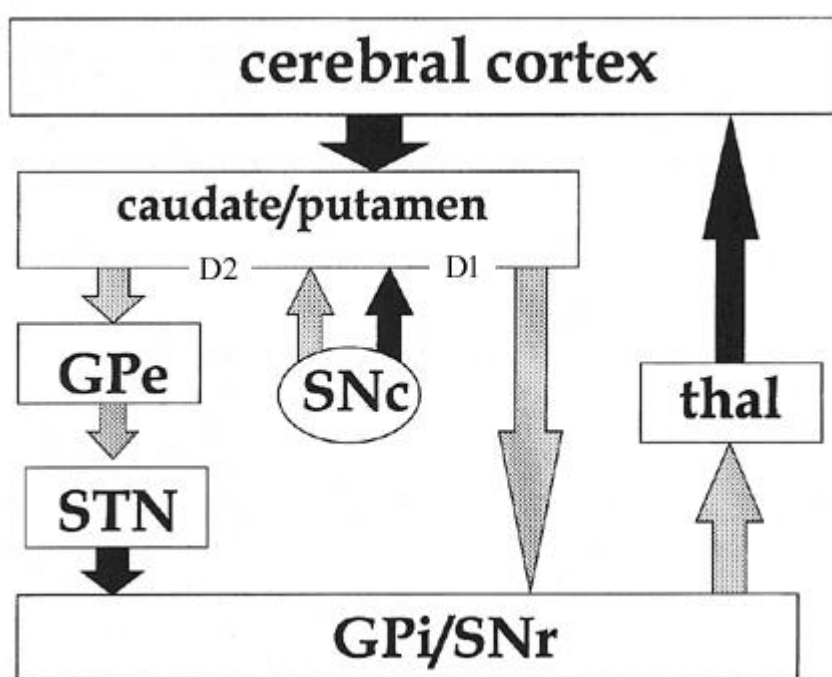
Δ – large aspiny cholinergic interneuron.

□ – medium-sized spiny GABAergic projection neuron that expresses D₂ receptors.



black arrows – *excitation*;
speckled arrows – *inhibition*.

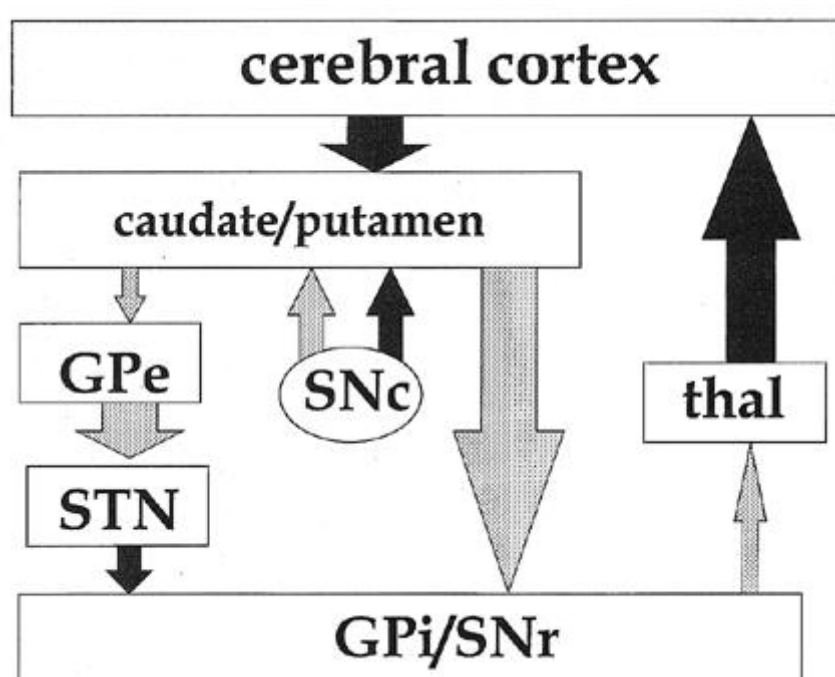
GP_i = globus pallidus internal segment;
GP_e = globus pallidus external segment;
STN = subthalamic nucleus;
SNr = pars reticularis of substantia nigra;
SNc = pars compacta of substantia nigra;
thal = thalamus.



- striatum acts via 2 pathways:
direct pathway inhibits GP_i / SNr;
indirect pathway stimulates GP_i / SNr.

HUNTINGTON DISEASE

1. Underactivity of GABAergic systems – due to loss of striatal medium spiny GABAergic neurons:
 - *lost striatal GABA efferents to GPe* (i.e. indirect pathway ↓) → subthalamic nucleus inhibition ↑ → thalamus is no longer inhibited → cortex overexcitation → **chorea!**
 - with disease progression, striatum may be completely devoid of cells (replaced by gliotic process) - *striatal efferents to GPi are also lost* → **akinetic-rigid state** and **dystonia**; chorea abates.



Progressive striatal atrophy is basis for staging.

2. Additional contributing intrastriatal findings - choline acetyltransferase (CAT) activity ↓ and Acch ↓, number of muscarinic receptors ↓ (i.e. **cholinergic** underactivity).
3. Overactivity of cerebral **glutamatergic** and striatal **dopaminergic** systems.

CLINICAL FEATURES

- begins insidiously during **ADULT LIFE** (often after affected individuals have already borne their children).
 - usually 35-40 years of age (but range is broad – from 5 to 70 years); ≈ 10% before age 20 yr.; < 1% before age 10 yrs.
 - inverse correlation between *number of CAG repeats* and *age at onset*.
- clinical manifestations vary among involved family members - patients may have predominantly **personality**, **cognitive**, or **movement** disorders – all three may occur together at onset or one may precede others by period of years.

Gradual onset of **chorea + dementia + behavioral abnormalities** in young / middle-aged **adult**

1. **MOVEMENT DISORDERS**

- **slowed eye saccades** are usually first sign; loss of smooth pursuit.
- **CHOREA** (predominant movement disorder in 85% patients) see p. Mov1 >>
 - starts as fine, irregular body jerks with no functional significance.
 - coordination, gait, and balance difficulties gradually supervene.
 - **dancing gait** is particularly characteristic see p. Mov7 >>
 - muscle hypotonia.
- terminally:
 - **choreic movements disappear** - replaced by **rigidity** and **dystonia**.
 - seizures are not unusual.
 - dysarthria, dysphagia, respiratory difficulties.

Juvenile form of HD (s. Westphal variant of HD) ($\approx 10\%$) – no chorea, progressive parkinsonism (rigidity, not muscle hypotonia!), dystonic postures, ataxia, seizures (!), myoclonus, dementia are more prominent.

Tendon reflexes normal (may be hyperactive); **plantar responses** may be abnormal.

Cranial nerves remain intact (except for rapid eye movements - impaired in large percentage of patients).

Sensation is unaffected.

2. **PSYCHIATRIC (PERSONALITY) DISTURBANCES:** emotional disturbances (may be severe → impulsiveness, fits of violence, bouts of mania / depression with suicidal ideation), delusions, paranoia, hallucinations, frank schizophrenic psychotic features.

N.B. $\approx 75\%$ patients initially present with psychiatric symptoms!

3. **COGNITIVE IMPAIRMENT** - source of major disability: memory difficulties, concentration problems, confusion; *eventually, patients become demented*.

- due to changes in both cerebral cortex and deep nuclei - frontostriatal dysfunction (i.e. SUBCORTICAL dementia).
- cognitive decline correlates pathologically / radiologically with degree of caudate atrophy / hypometabolism.
- Alzheimer patients do poorly on verbal and well on motor learning; vs. HD patients do well on **verbal** and poor on **motor** learning; PD patients perform poorly on both.

DIAGNOSIS

CHOREA + DEMENTIA + PERSONALITY DISORDER \pm FAMILY HISTORY

DNA testing - reliable diagnostic test!

- **preclinical and prenatal testing** can be possible without need to test other family members.
- test is positive if ≥ 38 repeats are found.
- diagnosis is "inconclusive" in those with **borderline number** of trinucleotide repeats, i.e. 34-37.
- presymptomatic patients who test positive respond similarly to patients with cancer when diagnosis is confirmed.
- International Huntington Association and World Federation of Neurology Research Group on Huntington's Disease have jointly issued guidelines on preclinical testing.
 - if adult with 25% risk for HD desires to be tested, but person's parent does not wish to know if he or she carries gene, guidelines state that adult with 25% risk has greater priority to know than does his or her parent to prevent testing.

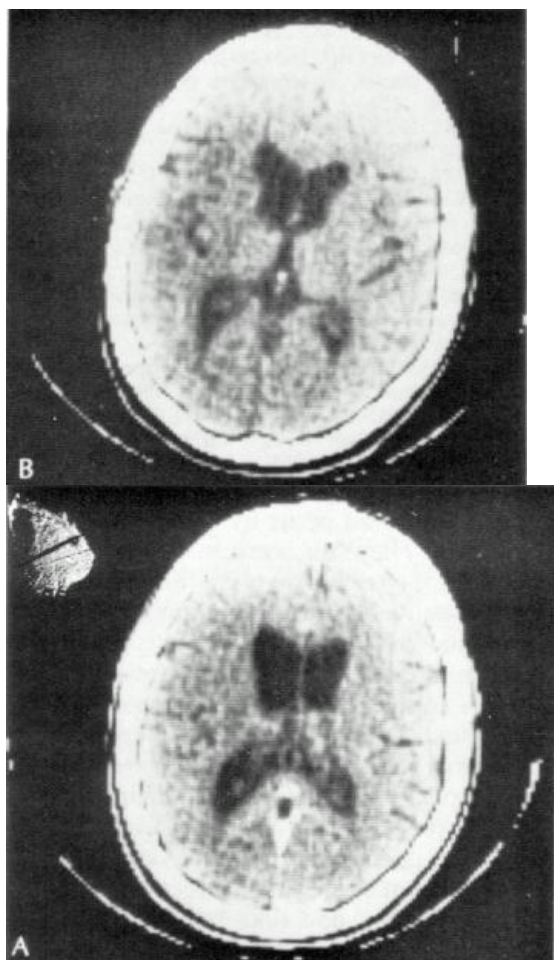
Genetic testing & counseling are extremely important, because 50% offsprings are at risk and disorder is not clinically manifest until after childbearing years.

EEG - generalized voltage attenuation.

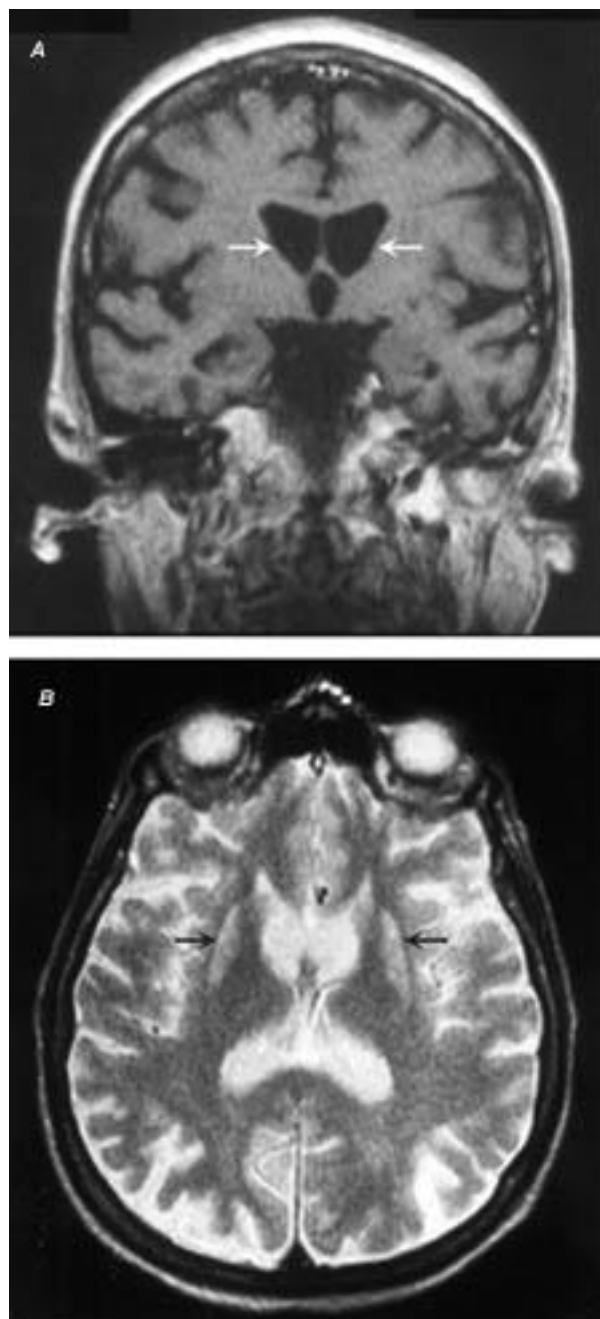
PET - **hypometabolism in striatum and cortex** (before atrophy of caudate nuclei is demonstrated on CT or MRI)

- severity of chorea correlates with **subcortical** metabolic activity;
- severity of dementia is linked to **cortical** metabolic rates.

MRI, CT – cerebral atrophy, **caudate (esp. head!!!) atrophy** → “ex vacuo” **enlargement of lateral ventricles** esp. anterior horns (“butterfly” or “boxcar” lateral ventricles).



MRI-T2 demonstrates abnormal high signal intensity in putamen:



TREATMENT

For disabling CHOREA, severe PSYCHOSIS - ANTIDOPAMINERGIC drugs:

- 1) **DA receptor-blockers** (e.g. **HALOPERIDOL**, **FLUPHENAZINE**)

- 2) **dopamine-depleters**, e.g. **TETRABENAZINE*** (most serious side effects – depression, suicidal thoughts/actions), **DEUTETRABENAZINE** (Austedo®)*, **RESERPINE**

*FDA-approved

- may not improve other symptoms.
- potentially serious side effects – parkinsonism, tardive dyskinesia (neuroleptics), depression (dopamine-depleters).
- attempts to **replace GABA deficiency** (by GABA-mimetics or inhibitors of GABA metabolism) have been unsuccessful.
- experimental therapies aim to **reduce glutamatergic neurotransmission** (via NMDA receptor blockage) and **bolster mitochondrial energy production**.

For **AFFECTIVE disorders** - **ANTIDEPRESSANTS** (tricyclic antidepressants, SSRI); may precipitate myoclonus!

Surgery – GPi **DBS**

Victoria Gonzalez “Deep brain stimulation for Huntington's disease: long-term results of a prospective open-label study” *Journal of Neurosurgery* Jul 2014 / Vol. 121 / No. 1 / Pages 114-122

GPi-DBS may provide sustained chorea improvement in patients with pharmacologically resistant chorea, with transient benefit in physical aspects of quality of life before progression of behavioral and cognitive disorders. DBS therapy did not improve dystonia or bradykinesia.

As disease advances, **confinement to psychiatric facility** becomes necessary.

PROGNOSIS

- **progressive** functional decline.
- **death** within 12-15 years of onset (more rapidly in those with earlier age of onset):
 - a) aspiration and inanition from severe dysphagia.
 - b) suicide (from depression) in up to 8% of males and 6% of females.

Westphal variant is fatal in < 10 years.

OTHER FORMS OF CHOREA

SYDENHAM'S CHOREA (ST. VITUS' DANCE, ACUTE CHOREA, CHOREA MINOR, RHEUMATIC CHOREA)

- described by Thomas Sydenham in 1686.
- **etiology** - **autoimmune disorder** after exposure to *Streptococcus pneumoniae* (most typically, as sequelae of rheumatic fever – chorea develops in ≈ 10% RF patients).
N.B. unlike arthritis and carditis, chorea **may not develop up to 12 months** after acute infection!
- 50% patients have IgG antibodies against neurons in caudate and subthalamic nuclei.
- **pathology** (primarily **striatum**) - edema, chromatolysis, atrophy.
- almost exclusively disease of childhood (ages 5-15).
- girls : boys = 2 : 1

CLINICAL PICTURE - child with **chorea** (in 80% generalized*), **hypotonia**, and **emotional lability**;

SYDENHAM CHOREA - movements more flowing, irregular, purposeless, with restless-appearing quality**; facial grimacing is common.
HUNTINGTON CHOREA - movements more individualistic and jerky.

- insidious onset.
- normal motor & sensory examination (sometimes pendulous knee jerk).
- **very distressed** in midst of chorea (rest poorly, can develop number of behavioral abnormalities).
- condition is usually **self-limited**; average duration – 3-6 weeks (up to 12 months); gradual cessation; **no neurologic residua**.
- recurrences (after months ÷ several years) in 35% cases (H: antistreptococcal prophylaxis as for rheumatic fever).
- susceptibility to *chorea gravidarum*, *chorea from oral contraceptives* are sequelae.
*ocular muscles are spared
**vs. hyperkinetic children - movements are purposeful

DIAGNOSIS

- 1) **EEG** - diffuse slowing or nonspecific dysrhythmias.
- 2) **PET** - striatal hypermetabolism (vs. other types of choreic disorders).
- 3) laboratory evidence of **previous streptococcal infection** (may be already absent).

TREATMENT

(during period of marked chorea):

- 1) **bed rest** in **quiet room**; sedatives (e.g. **benzodiazepines**) may be needed.
- 2) **dopamine-blocker** (**HALOPERIDOL**, **RISPERIDONE**), **dopamine-depletor** (**RESERPINE**).
- 3) **corticosteroids** may accelerate recovery.

N.B. **back to school ASAP** (many of so called psychologic effects previously ascribed to chorea were due not to disease itself, but to associated deprivation and patient's anxiety)!

OTHER IMMUNE CHOREAS

SYSTEMIC LUPUS ERYTHEMATOSUS

- chorea is intermittent.
- no caudate hypometabolism on PET.
- treatment - antidopaminergic agents.

PRIMARY ANTIPHOSPHOLIPID ANTIBODY SYNDROME

- CNS is involved with strokes, multi-infarct dementia, and chorea.
- spontaneous remission occurs frequently.

CHOREA GRAVIDARUM, BIRTH CONTROL PILL CHOREA

- ESTROGENS are **dopamine facilitators** (either direct at receptor sites or through second messengers).
- **prior Sydenham's chorea** may be risk factor.

TREATMENT

- benzodiazepines in 2nd and 3rd trimesters.

- avoid D receptor-blocking drugs in pregnancy (particularly during limb-genesis period in 1st trimester).

SENILE CHOREA

- insidiously begins after age 60.
- mild, isolated chorea; usually involves limbs.
- slow progression is possible.
- no neurobehavioral symptoms, no family history of chorea.
- some have predominantly *caudate* atrophy (not to degree seen in HD), some - *putamen* atrophy.
- no degenerative changes in cerebral cortex.

NEUROACANTHOCYTOSIS

- INHERITANCE - autosomal dominant, recessive, or even X-linked.
- most common hereditary chorea after HD.

CLINICAL FEATURES

- 1) generalized **CHOREA** (less severe than in HD), motor and vocal tics, dystonia, parkinsonism.
 - 2) one of most distinguishing features – **FEEDING DYSTONIA** due to orolingual dystonia (*food expulsion from mouth by protruding tongue, lip & tongue-biting* - self-mutilating behavior).
 - 3) amyotrophy, areflexia.
- onset in 3rd-4th decade, but range is wide (8 to 62 years).
 - death within 15 years of diagnosis.

DIAGNOSIS

- **ACANTHOCYTES** (> 15% of all RBCs) in fresh blood smears;
 - erythrocytes may require *incubation* in 1 : 1 normal saline for 3-5 min prior to wet mount preparation.
 - mechanism of acanthocyte formation is unknown (abnormal protein to fatty acid ratios?, abnormal erythrocyte surface antigens?).
- **creatinine phosphokinase (CK)**↑
- **CT / MRI** - caudate atrophy (very similar to Huntington's disease)
- **PET** - putaminal and caudate fluorodopa uptake↓, D₂ receptor density↓

TREATMENT

- **antidopamine:**
 - a) dopamine-blocking drugs (haloperidol, fluphenazine)
 - b) dopamine-depleting drugs (reserpine, tetrabenazine).

HEMICHOREA & HEMIBALLISM

- chorea / ballism to one side of body.

ETIOLOGY - destructive lesion of contralateral subthalamic nucleus or its connections

- a) **stroke** – abrupt onset in middle-aged or elderly patients; may be preceded by hemiplegia hemiparesis (choreic or ballistic movements appear when return of motor function occurs).
 - b) **tumor** in subthalamic nucleus
 - c) **unsuccessful thalamotomy** (when target was missed).
- movements tend to diminish over time.
 - treatment – antidopaminergic drugs.

HEREDITARY NONPROGRESSIVE CHOREA

- autosomal dominant pattern; begins in childhood.
- nonprogressive chorea, which lessens in severity over time.
- no other neurologic problems.
- **PET** - striatal hypometabolism.

BIBLIOGRAPHY for ch. "Movement disorders, Ataxias" → follow this [LINK >>](#)