

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 $\uparrow\downarrow$, 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 \uparrow 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):

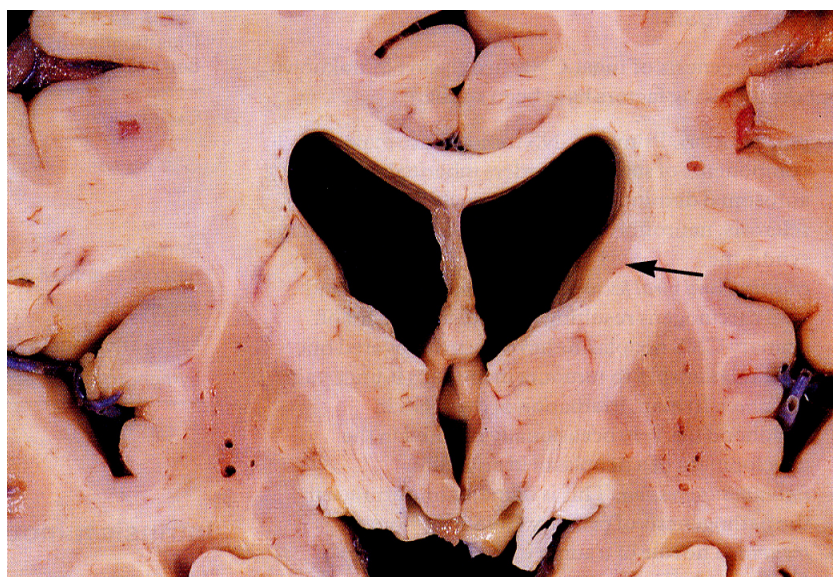
1. Neuron loss in **cortex** (especially in layer 3) - frontal lobe, less often in parietal lobe, and occasionally in entire cortex.
2. **Most severe atrophy in striatum** (particularly caudate nucleus) - severe loss of **medium spiny projection neurons** with their **GABAergic striatal efferents**.
 - **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.

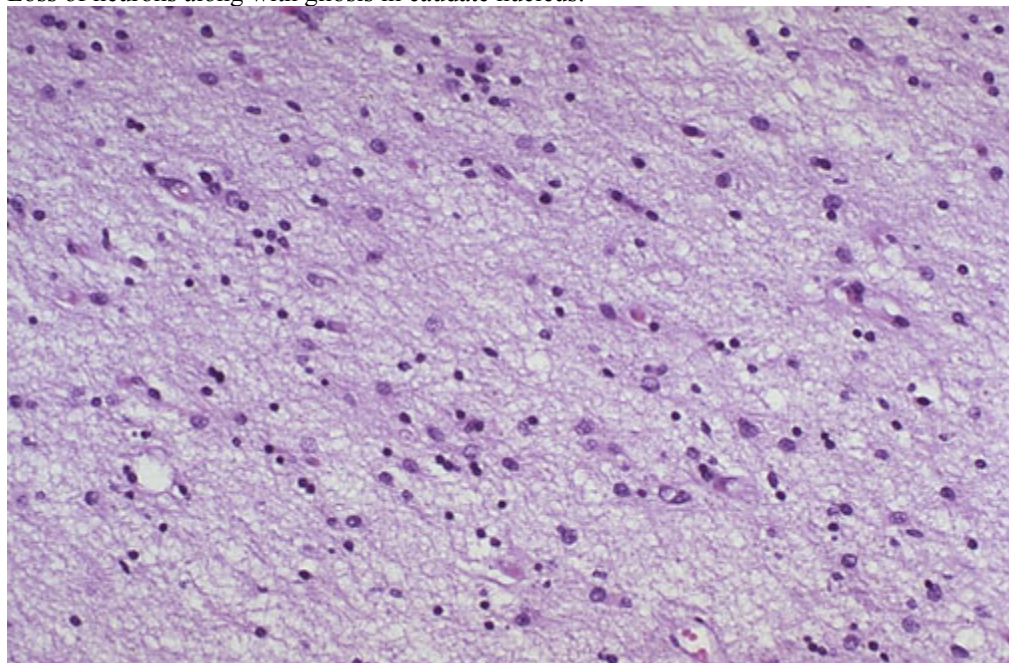
Atrophy of caudate nucleus and dilatation of lateral ventricle:



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) >>

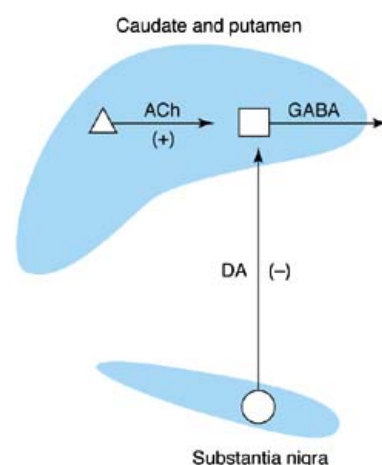


PATHOPHYSIOLOGY

NORMA see p. A103 >>

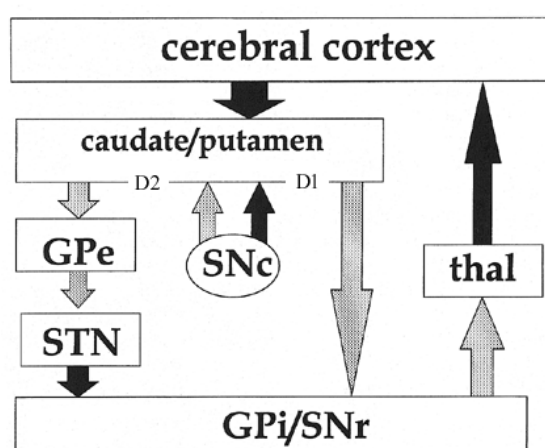
DA neurons inhibit (via D₂ receptors) and **ACh neurons excite** GABAergic output from striatum:

- Δ – large aspiny cholinergic interneuron.
- – medium-sized spiny GABAergic projection neuron that expresses D₂ receptors.



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

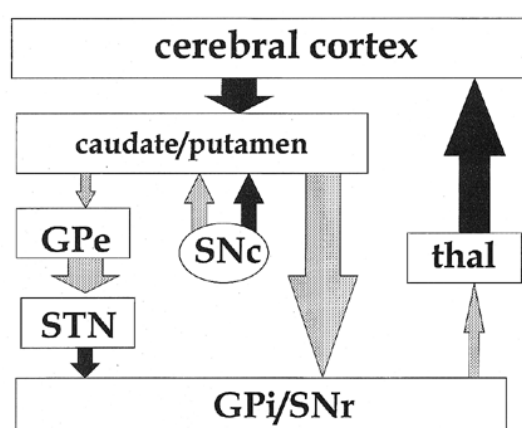
GP_i = globus pallidus internal segment;
 GP_e = globus pallidus external segment;
 STN = subthalamic nucleus;
 SNr = pars reticularis of substantia nigra;
 SNc = pars compacta of substantia nigra;
 thal = thalamus.



- 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) (≈ 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. ≈ 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 ± 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.

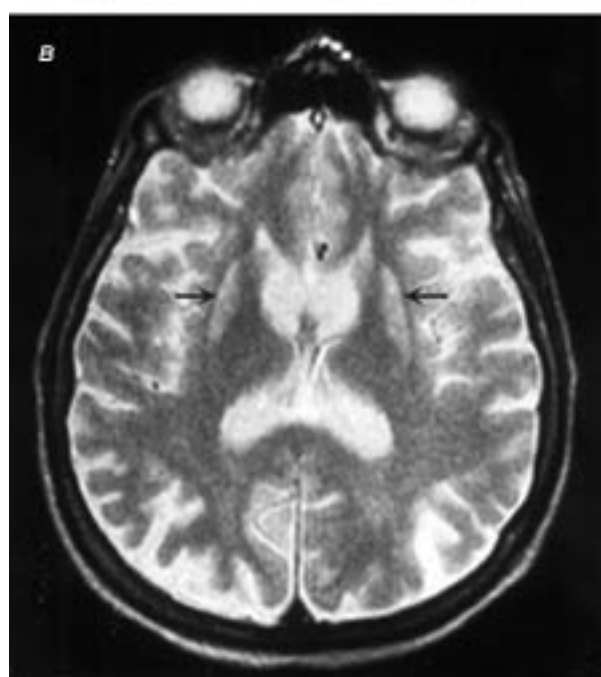
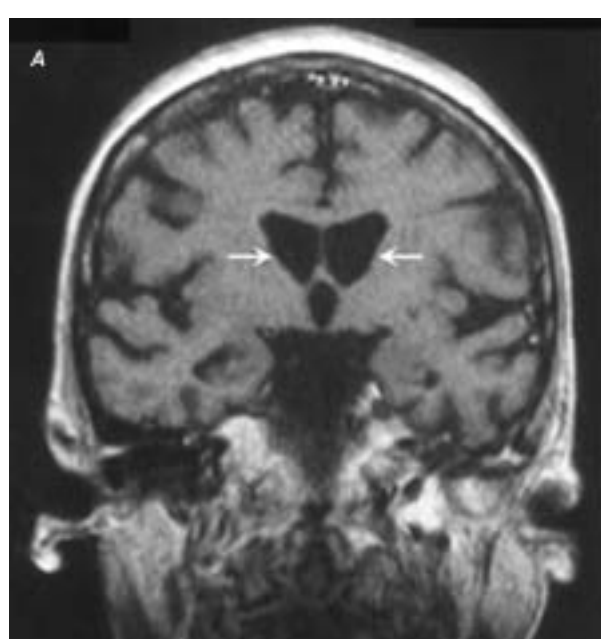
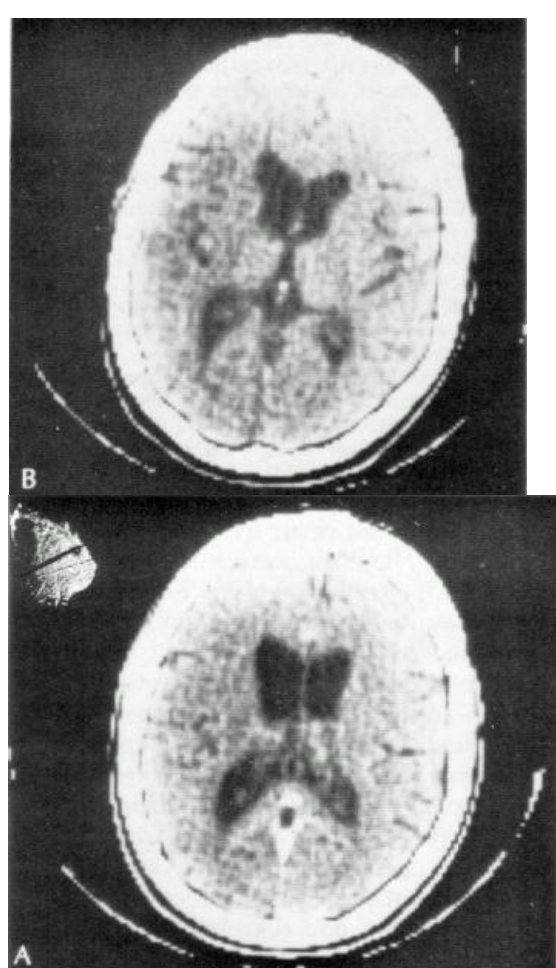
Genetic testing & counseling are extremely important, because 50% offsprings are at risk and disorder is clinically manifest until after childbearing years.

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***, **RESERPINE**)

*FDA-approved; most serious side effects – depression, suicidal thoughts-actions

- 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!

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.
- **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](#) >>

Viktor's NotesSM for the Neurosurgery Resident
Please visit website at www.NeurosurgeryResident.net