Choreas

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Etiological Classification Of Chorea

1. Huntington Disease (HD)

Pathogenesis

1. Pathogenesis

2. Pathophysiology

3. Huntington disease

Clinical Features

4. Diagnosis

5. Treatment

6. Prognosis

Other Forms of Chorea

Sydenham's chorea (St. Vitus' dance, acute chorea, chorea minor, rheumatic chorea)

Diagnosis

Treatment

Other Inimmune Choroes

Chorea gravidarum, Birth Control Pill Chorea

Treatment

Soule chorea

Neuroacanthocytosis

Clinical Features

Diagnosis

Hemicheora & Hemiballism

Hereditary Nonprogressive Chorea

Etiological Classification of Chorea

1. Hereditary choreas
   a. Huntington's disease
   b. benign hereditary chorea - nonprogressive chorea in childhood.
   c. neuroacanthocytosis
   d. other CNG "degenerations": olivopontocerebellar atrophy, Azorean disease, ataxia telangectasia, tuberous sclerosis, Hallervorden-Spatz disease, dentato-rubral-pallido-luysian atrophy (DRPLA), familial calcification of basal ganglia.

2. Developmental & aging choreas
   a. physiological chorea of infancy
   b. cerebral palsy (anoxic, kernicterus)
   c. minimal cerebral dysfunction
   d. buccal-oral-lingual dyskinesia and edentulous orodyskinesia in elderly
   e. senile chorea (probably several causes)

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

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

5. Metabolic causes
   a. hyperthyroidism
   b. hypoparathyroidism (various types)
   c. pregnancy (chorea gravidarum)
   d. NA\textsubscript{1}, Mg\textsubscript{1}, Ca\textsubscript{1}
   e. hypo- and hyperglycemia (latter may cause hemichorea, hemibalism)
   f. acquired hepatic cerebral degeneration
   g. nutritional (e.g. beriberi, pellagra, vitamin B\textsubscript{12} deficiency in infants)

6. Infections / immunologic causes
   a. Sydenham's chorea
   b. eiccephalitis lethargica
   c. various other infections / postinfectious encephalitides (incl. Creutzfeldt-Jakob disease)
   d. 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

Antisomalous 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 = 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 codons for glutamine - increase in polyglutamine causes IT15 gene overexpression - protein is termed HUNTINGTIN.
CHOREAS

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- 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:

Loss of neurons along with gliosis in caudate nucleus:
PATHOPHYSIOLOGY

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

\[ \Delta \text{ – large aspiny cholinergic interneuron.} \]
\[ \square \text{ – medium-sized spiny GABAergic projection neuron that expresses D}_2\text{ receptors.} \]

Black arrows – excitation; speckled arrows – inhibition.

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

**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 \( \downarrow \)) \[ \text{subthalamic nucleus inhibition} \downarrow \Rightarrow \text{thalamus} \downarrow \Rightarrow \text{cortex overexcitation} \Rightarrow \text{chorea}! \]
   - with disease progression, striatum may be completely devoid of cells (replaced by gliotic process) \[ \text{striatal efferents to GPi are also lost} \Rightarrow \text{akinetic-rigid state and dystonia; chorea abates.} \]

   Progressive striatal atrophy is basis for staging.

2. Additional contributing intrastriatal findings - choline acetyltransferase (CAT) activity\( \downarrow \) and Ach\( \downarrow \), number of muscarinic receptors\( \downarrow \) (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); \( \approx 10\% \text{ before age 20 yr.;} \text{ < 1\% before age 10 yrs.} \)
  - 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) 
  - starts as fine, irregular body jerks with no functional significance.
  - coordination, gait, and balance difficulties gradually supervene.
  - Muscle hypotonia.
- Terminaly: 
  - choreic movements disappear - replaced by rigidity and dystonia.
  - seizures are not unusual. 
  - dysarthria, dysphagia, respiratory difficulties.
- 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, bount of mania / depression with suicidal ideation), delusions, paranoia, hallucinations, frank schizophrenic psychotic features.

- Juvenile form of HD (≈ 10%) - no chorea, progressive parkinsonism (rigidity, not muscle hypotonia!), dystonic postures, ataxia, seizures (!), myoclonus, dementia are more prominent.

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.
- Preclinical and prenatal testing can be possible without need to test other family members.
- International Huntington Association and World Federation of Neurology Research Group on Huntington’s Disease have jointly issued guidelines on preclinical testing.

EKG - generalized voltage attenuation.

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

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

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), DEUTERABENAZINE (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 SMDA receptor blockade) and bolster mitochondrial energy production.

For AFFECTIVE disorders – ANTIDEPRESSANTS (tricyclic antidepressants, SSRIs); may precipitate myoclonus?

Surgery – GPi: DBS


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.
• enolgy – autoimmune disorder after exposure to Streptococcus pneumonia (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.
• paroxysm (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 non-specific dysrhythmias.
2) PET – striatal hypometabolism (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 (TIAUPPERN® (DESPERINE®), dopamine-depleter (RESERPINE)).
3) curtiostrenoids 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 - antidiopaminergic 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

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

**SENILE CHOREA**

- insidiously begin 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?).

- creatine 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.