What is chorea?

- Rapid, multi-focal, irregular movements
- Usually flitting between various muscle groups in different body parts
- When mild, may just appear restless
- Motor impersistence
- In fingers, for example, “piano-playing”
Evaluation of the patient with chorea

• Family history
• Time course
• Phenomenology
• Exacerbating/relieving factors
• Other neurological features
• Other medical conditions
• Medications
• Neuroimaging and laboratory work-up
Evaluation of the patient with chorea

- Family history/ethnic background
- Time course
- Phenomenology
- Exacerbating/relieving factors
- Other neurological features
- Other medical conditions
- Medications
- Neuroimaging and laboratory work-up
Family history positive

- Autosomal dominant
- Autosomal recessive
- X-linked
- Mitochondrial
Family history negative
- does not exclude genetic etiology

- Decreased penetrance
- Non-paternity
- Parental death prior to disease manifestation or unknown parental medical history
- *De novo* mutations
- AR disorders in small families
Chorea: autosomal dominant

- HD
- \textit{C9orf72} expansions
- HDL1 (prion disease; single family)
- HDL2 (African ancestry)
- Spinocerebellar ataxias, esp. SCA 1, 2, 3, 17, (SCA 17=HDL4)
- Dentatorubropallidoluysian atrophy (mainly, but not exclusively, Japanese)
- Benign hereditary chorea
- Neuroferritinopathy (one of the NBIA disorders)
- “Fahr’s disease” - idiopathic basal ganglia calcification (\textit{SLC20A2}, \textit{PDGFRB}, \textit{PDGFB}) and other loci
- Paroxysmal dyskinesias
Huntington’s disease

• Autosomal dominant
• Huntingtin; *htt* 4p16.3 - function still unknown
• Expanded CAG repeats
• Complete penetrance of disease with >40 repeats
• Anticipation – younger age of onset with successive generations, due to expansion of repeat size
• Greater expansion with paternal inheritance
• Environmental and epigenetic factors in age of onset
• Pre-symptomatic psychological changes
• At present, diagnosis is made with appearance of unequivocal motor signs
Huntington’s disease

- 27-35 repeats unstable - can expand with transmission
- ?disease with <35 repeats – can expand in next generation.
- Apparent disease with 29 repeats (pathologically confirmed)
- Pre-mutation 36-39 repeats – decreased penetrance, late onset – probably accounts for “senile chorea” - expands in next generation
- Should be part of first-line testing - **but do not neglect genetic counselling even if the level of suspicion is low!**
C9orf72 disease

- Autosomal dominant
- Large hexanucleotide repeat expansions GGGG GCC
- Commonest cause of familial and sporadic ALS and frontotemporal dementia in many populations
- Most common cause of huntingtonism in the UK (2% of HD-negative subjects; Hensman Moss et al., 2014)
- Variable phenotypes – even within families
- Incomplete penetrance
- Age of onset - childhood - late adulthood
- Early behavioural and psychiatric problems
- Chorea, dystonia, myoclonus, tremor, parkinsonism
- Upper motor neuron signs
- Phenotype not related to size of expansion
- Stay tuned for more information on this disorder!
Huntington’s Disease-like 2

A Disorder Similar to Huntington’s Disease Is Associated with a Novel CAG Repeat Expansion

Russell L. Margolis, MD,1,2 Elizabeth O’Hearn, MD,3,4 Adam Rosenblatt, MD,1 Virginia Willour, PhD,1
Susan E. Holmes, PhD,1 Mary L. Franz, MSW,1 Colleen Callahan, BA,1 Hyon S. Hwang, BA,1
Juan C. Troncoso, MD,3,5 and Christopher A. Ross, MD, PhD1,2,4

Ann Neurol 2001;50:373–380

- Autosomal dominant inheritance
- African ancestry in all cases to date (although may not be apparent)
- Expanded trinucleotide (CTG) repeats within junctophilin-3 gene
- Chorea/dementia onset in 3rd-4th decade (age inversely related to size of expansion, as HD)
- Pathology very similar to HD
- Acanthocytosis seen in 10% of cases
Huntington’s disease-like 2

- Onset at 34 with personality change, chorea
- Examination aged 54
- Death aged 56
- Acanthocytosis
Benign hereditary chorea

- Autosomal dominant
- 14q (DeVries et al ’00), thyroid transcription factor 1 - TITF1
- Large deletions cause brain-thyroid-lung syndrome
- Other genes/linkage sites also
- No dementia
- Phenotype may include dystonia, myoclonus
- Some cases have developmental delay, short stature
- Decreased striatal interneurons (Kleiner-Fisman et al. 2005)
- Functional imaging suggests decreased D2 receptor binding (Konishi et al. 2012)
- But - benefit has been reported to both l-dopa and dopamine agonists, and tetrabenazine!
- But - not always benign, and not just chorea

Video courtesy of Dr. A. Perez Sempere; Sempere et al., J. Neurol. 2012
X-linked

- Filipino males - Lubag (DYT3), island of Panay, Capiz province
  - Dystonia-parkinsonism typical
  - Tremors, chorea, myoclonus also seen
  - Female carriers may be symptomatic
- Lesch-Nyhan (childhood, self-mutilation)
- McLeod syndrome
Chorea: autosomal recessive

- Neurodegeneration with brain iron accumulation (NBIA) disorders - aceruloplasminemia, phospholipase-associated neurodegeneration (PLAN)
- Wilson’s disease
- Autosomal recessive ataxias; Friedreich’s ataxia; ataxia-telangiectasia; ataxia with oculomotor apraxia 1, 2
- Chorea-acanthocytosis
- Infantile bilateral striatal necrosis
- HDL3 - (Kambouris et al ’00) (one family)
- Other pediatric metabolic disorders (glutaric aciduria, ….)
Evaluation of the patient with chorea

- Family history
- **Time course**
- Phenomenology
- Exacerbating/relieving factors
- Other neurological features
- Other medical conditions
- Medications
- Neuroimaging and laboratory work-up
Time course of symptoms

- **Sudden onset** – stroke, hemorrhage
- **Sub-acute onset** – metabolic, related to other medical conditions or medications, paraneoplastic syndrome, prion disease, tumour
- **Chronic, slowly progressive** – neurodegenerative
- **Chronic, non-progressive** – medication-induced, benign hereditary chorea
- **Episodic** - paroxysmal dyskinesias
Post-stroke hemichorea

• Onset at time of stroke
• Posterior limb of left internal capsule (basal ganglia)
• Video 5 months after stroke
• Benefit from carbamazepine 400mg bid
• Gradually resolved with time
Evaluation of the patient with chorea

- Family history
- Time course
- **Phenomenology**
- Exacerbating/relieving factors
- Other neurological features
- Other medical conditions
- Medications
- Neuroimaging and laboratory work-up
Phenomenology of chorea

- Distribution
  - trunk, neck, limbs
  - orofacial (tardive dyskinesia, chorea-acanthocytosis, acquired hepatocerebral degeneration)
Chorea: structural/metabolic causes

- Cerebral palsy
- Post-pump chorea (pediatric, rarely adult)
- Stroke
- Other vascular; AVM, vasculitides, moyamoya, cavernous angioma
- Tumour
- Multiple sclerosis
- Diabetic non-ketotic hyperglycemia (older women, more common in Asians); typical hyperintensity in contralateral putamen on T2-weighted MRI
• 87 year old woman
• Sudden onset hemichorea x 4 weeks
• No other known medical conditions
• Negative imaging

video
courtesy of Dr. S. Frucht
• Hgb = 15.4; elevated red cell distribution width; **polycythemia rubra vera**
• +JAK2 mutation
• Mechanism - likely related to basal ganglia ischemia

2 weeks later after
  - Phlebotomy x 2;
    Hgb = 14.5
  - Hydroxyurea
Evaluation of the patient with chorea

- Family history
- Time course
- Phenomenology
- **Exacerbating/relieving factors** (paroxysmal dyskinesias; e.g. movement, fatigue, caffeine)
- Other neurological features
- Other medical conditions
- Medications
- Neuroimaging and laboratory work-up
Evaluation of the patient with chorea

- Family history
- Time course
- Phenomenology
- Exacerbating/relieving factors
- **Other neurological features**
- Other medical conditions
- Medications
- Neuroimaging and laboratory work-up
Suggestive features on exam

- Asymmetry, localizing signs – structural lesion, or non-ketotic hyperglycemia
- Cognitive impairment, especially sub-cortical dementia, frontal signs – neurodegenerative disorder
- Ataxia – spinocerebellar ataxias (SCA 1, 2, 3, 17); DRPLA; autosomal recessive ataxias
- Decreased reflexes – chorea-acanthocytosis, McLeod syndrome
- Seizures – young-onset HD, parox. kinesogenic dyskinesia, McLeod syndrome, chorea-acanthocytosis
Suggestive features on exam

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• Decreased reflexes – chorea-acanthocytosis, McLeod syndrome
• Seizures – young-onset HD, parox. kinesogenic dyskinesia, McLeod syndrome, chorea-acanthocytosis
Spinocerebellar ataxia 2

• No FH
• Diagnosed with schizophrenia aged 25
• Dysarthria and stuttering aged 28
• Gait difficulty, impaired balance
• Decreased reflexes and vibration
• Eye movements normal
• Chorea aged 31
• MRI – mild cerebellar atrophy
• SCA 2 22/39 repeats (normal <31)
Suggestive features on exam

- Asymmetry, localizing signs – structural lesion, or non-ketotic hyperglycemia
- Cognitive impairment, especially sub-cortical dementia, frontal signs – neurodegenerative disorder
- Ataxia – spinocerebellar ataxias (SCA 1, 2, 3, 17); DRPLA; AR ataxias
- Decreased reflexes – chorea-acanthocytosis, McLeod syndrome
- Seizures – chorea-acanthocytosis, McLeod syndrome
Chorea-acanthocytosis (AR)

- 9q21 – *VPS13A* (formerly *CHAC*)
- Protein - chorein
- Onset 20-40 yrs
- Behavioural changes, psychiatric symptoms, dementia
- Chorea, dystonia, oro-lingual dyskinesias (self-mutilation), parkinsonism, tics
- Seizures
- Peripheral neuropathy and myopathy
- **Elevated creatine kinase, liver enzymes**
Acanthocytosis

- Variably present for reasons which are unclear
- Membranes can be deformed induced by stressing RBCs
- EM of glutaraldehyde-fixed cells is gold standard
- Don’t confuse with echinocytes
- Although intermediate forms can be seen
- Absence of acanthocytes does not exclude a neuroacanthocytosis syndrome
Chorea-acanthocytosis

- 31 y/o man with gait difficulty
- No family history
- Developed psychotic depression aged 20
- Gait difficulty and involuntary movements for 3 years
- One seizure
- Distal sensory loss
- Tics (vocal), dropping things
- Head pulls to right
- Occasional falls
- Weight loss
- Problems with eating
- Forgetfulness, poor judgment, e.g. when crossing the street, not taking care of appearance, compulsive shopping and listening to music loudly
Western blot showed absence of chorein: chorea-acanthocytosis (autosomal recessive)
Orofacial dyskinesia, self-mutilations in chorea-acanthocytosis

Courtesy Dr Jane Zheng, UNC-CH
Levine-Critchley syndrome

IN THE Bassen-Kornzweig syndrome, a thorny malformation of the erythrocytes (acanthocytes), a disease which begins in childhood, is associated with progressive ataxia; stigmata of retinal pigmentosa; muscle wasting; steatorrhea, which may appear only in early life; and biochemical abnormalities. The serum levels of cholesterol, carotene, vitamin A, and phospholipids are invariably depressed, and the β-lipoprotein moiety is absent. This syndrome appears to be the expression of an autosomal recessive gene.

The family described in this paper is not the first in which acanthocytosis in an adult has been reported in conjunction with neurological disease, but the neurological manifestations are dissimilar to those of the Bassen-Kornzweig syndrome, and the biochemical abnormalities of that syndrome are not present. Koo and Bassett in 1962 reported steatorrhea, acanthocytosis, and neuroropathy in a man aged 41, but the nature of the neuropathy was not commented upon. Kahani et al., 1963, noted "acquired" acanthocytosis in a patient with Eales' disease and also reported two families in which hereditary vitreoretinal degeneration (degeneratio hyaloides orbitale) was associated with acanthocytosis. It is still not certain whether the cells described in Kahan's patients were acanthocytes or crenated erythrocytes. More recently, Lewis et al. (11) and Mars et al. (12) from Cleveland have reported the biochemical abnormalities and the neurological findings in a 30-year-old patient with a pattern of disease quite dissimilar to that of the present family. The salient clinical features found in their patient were fat intolerance, impaired sphincter control, cerebellar incoordination, hyperactive reflexes, and hypoproteinemia.

Acanthocytosis and Neurological Disorder

Betalipoproteinemia

E. M. R. Critchley, BM, MRCP; David B. Clark, MD; and Abraham Wittler, MD, Lexington, Ky

Report of Cases

Nestologically affected members of this family lie within two generations. The proband (F. 10), a 29-year-old white man from eastern Kentucky who belongs to the first generation, was seen some 3½ years ago and exhibited at that time involuntary movements and a grossly swollen, raw, bitten tongue (Fig 1). He had had 15 to 20 similar episodes of tongue, lip, and cheek biting, which occurred at night. The episodes had begun six years earlier on a background of increasing general weakness, nervousness, "fits and jerks," and had increased in frequency and severity. The involuntary movements included finger-snapping, grimacing, dystonic and choreiform movements, hyperextension of the trunk, winking, pouting, and crosswise and droulling. Cogadala, seen in the Gilles de la Tourette syndrome, was not evident. There had been times when he could not speak plainly; "the inside of his mouth would draw," he would "snap at his lips, and his stomach would stick." When he ate, his tongue would involuntarily push his food out onto his plate. Since 1962 he had preferred to retire to a separate room to eat his food.

He was alert, well-oriented, had no gross memory defects or psychotic behavior, and was disturbed by his own repetitive appearance. He startled and stuttered a little when talking and had occasional inappropriate laughter. Despite the frequent involuntary movements, there was no ataxia of gait, and finger-nose, finger-finger, and heel-shin coordination tests were intact. He had generalized hypotonia, flexor plantar responses, and loss of deep tendon reflexes.

His symptoms conformed, for the most part, to the tentative diagnosis of Huntington's chorea. His full-scale intelligence quotient was 72 (Wechsler Adult Intelligence Scale (WAIS), verbal 81, and performance 61. The electro-
Levine-Critchley syndrome

IN THE Bassen-Kornzweig syndrome, a thorny malformation of the erythrocytes (acanthocytes), a disease which begins in childhood, is associated with progressive ataxia; atypical retinitis pigmentosa; muscle wasting; statorrhea, which may appear only in early life; and biochemical abnormalities. The serum levels for cholesterol, carotenoids, vitamin A, and phospholipids are invariably depressed, and the α-lipoprotein moiety is absent. This syndrome appears to be the expression of an autosomal recessive gene.

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Submitted for publication June 10, 1967; accepted June 24.
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Acanthocytosis Without

Neurological Disorder

F. M. R. Critchley, BM, MRCP; David B. Clark, MD; and Abraham Witter, MD, Lexington, Ky

Report of Cases

Neurologically affected members of this family lie within two generations. The proband (1.10), a 29-year-old white man from eastern Kentucky who belongs to the first generation, was seen some 2½ years ago and exhibited at that time involuntary movements and a grossly swollen, raw, bitten tongue (Fig 1). He had had 15 to 20 similar episodes of tongue, lip, and cheek biting, which often occurred at night. The episodes had begun six years earlier on a background of increasing general weakness, nervousness, "its and jerks," and had increased in frequency and severity. The involuntary movements included finger-snapping, grimacing, dystonic and choreiform movements, hyperextension of the trunk, marking noises, pleural sounds, and drooling. Copedellala, seen in the Gilles de la Tourette syndrome, was not evident. There had been times when he could not speak plainly; "the inside of his mouth would draw," he would "snap at his lips, and his stomach would stick." When he ate, his tongue would involuntarily push his food out onto his plate. Since 1962 he had preferred to retire to a separate room to eat his food.

He was alert, well-oriented, had no gross memory defects or psychotic behavior, and was disturbed by his own repetitive appearance. He slurred and stuttered a little when talking and had occasional inappropriate laughter. Despite the frequent involuntary movements, there was no ataxia of gait, and finger-nose, finger-finger, and heel-shin coordination tests were intact. He had generalized hypotonia, flexor plantar responses, and loss of deep tendon reflexes.

His symptoms conformed, for the most part, to the tentative diagnosis of Huntington's chorea. His full-scale intelligence quotient was 72 (Wechsler Adult Intelligence Scale (WAIS), verbal 81, and performance 61. The electro-
Chorea-Acanthocytosis Genotype in the Original Critchley Kentucky Neuroacanthocytosis Kindred

Antonio Velayos-Baeza, PhD; Elke Holinski-Feder, MD, PhD; Birgit Neitzel; Benedikt Bader, MD; Edmund M. R. Critchley, DM(Oxon), FRCP; Anthony P. Monaco, MD, PhD; Adrian Danek, MD; Ruth H. Walker, MB, ChB, PhD

Arch Neurol. 2011;68(10):1330-1333

- Only one mutation found throughout extended family
- Haplotype analysis demonstrates that same mutation likely to have been inherited from both parents
- Levine’s family has been lost to follow-up
X-linked

- McLeod syndrome
- Lubag (DYT3)
- Lesch-Nyhan (childhood, self-mutilation)
McLeod syndrome

- *XK* gene on Xp21
- absent Kx ag; reduced Kell antigens
- Onset 20 yrs onwards, but most 40-60 yrs
- Chorea, dystonia, tics, parkinsonism, (lip-biting rare)
- Seizures
- Behavioural change, psychiatric symptoms, dementia
- Peripheral neuropathy (mild), myopathy, elevated CK
- Cardiomyopathy; CHF; dysrhythmias – atrial fibrillation, flutter - cause of sudden death
- Hepatosplenomegaly, elevated LFTs
Evaluation of the patient with chorea

- Family history
- Time course
- Phenomenology
- Exacerbating/relieving factors
- Other neurological features
- **Other medical conditions**
- Medications
- Neuroimaging and laboratory work-up
Autoimmune causes

- Sydenham’s chorea (ASO, anti-DNase B)
- Lupus (lupus anti-coagulant)
- Systemic sclerosis
- Anti-phospholipid ab (anti-cardiolipin) syndrome
- Paraneoplastic; renal, small-cell lung, breast, Hodgkin’s, non-Hodgkin’s lymphoma (anti-Hu, anti-CRMP5, anti-Yo, anti-Caspr2, anti-GAD65, anti-NMDA receptor, anti-LG1-1, anti-striational?......)
- Non-paraneoplastic; anti-LGI-1, anti-Caspr2
- Coeliac disease
Coeliac-associated chorea

- Aged 60; involuntary movements x 1 yr
- No family history; father died aged 56
- +coeliac disease, elevated anti-gliadin abs
Evaluation of the patient with chorea

- Family history
- Time course
- Phenomenology
- Exacerbating/relieving factors
- Other neurological features
- Other medical conditions
- **Medications**
- Neuroimaging and laboratory work-up
Chorea: drug-induced (1)

• Levo-dopa-induced dyskinesia in Parkinson’s disease (peak dose; on-off)
• Direct drug effect; cocaine, amphetamine, anticonvulsants, Li, and other stimulants
• Estrogens (oral contraceptives, hormone replacement therapy) – may worsen underlying condition e.g. chorea-acanthocytosis
Chorea: drug-induced (2)

- Tardive (typical neuroleptics, anti-convulsants, Li, SSRIs)
- Use of neuroleptics for psychiatric symptoms may mask appreciation of movement disorder due to neurodegenerative etiology (HD, C9ORF72, HDL2, chorea-acanthocytosis, McLeod)
Evaluation of the patient with chorea

- Family history
- Phenomenology
- Time course
- Exacerbating/relieving factors
- Other neurological features
- Other medical conditions
- Medications
- Neuroimaging and laboratory work-up
CT/MRI findings

- Structural lesion
- **Iron deposition = Neurodegeneration with brain iron accumulation (NBIA).** Only 2 typically cause chorea in adults -
  - Neuroferritinopathy (AD)
  - Aceruloplasminemia (AR)
- **Calcium deposition (“Fahr’s disease”)**
  - chorea, parkinsonism, dystonia, ataxia, dementia
  - idiopathic basal ganglia calcification (*SLC20A2 PDGFRB, PDGFB*) and other loci
  - may also be mitochondrial
Treatment of chorea (1)

• Treat underlying cause (if appropriate)
• Symptomatic; may not result in functional improvement
• Dopamine-depleting agents; tetrabenazine, reserpine
• Dopamine-blocking agents; atypical neuroleptics
• Anticonvulsants; valproate, carbamazepine, levetiracetam (may worsen chorea!)
• Glutamate NMDA-receptor antagonists; amantadine, riluzole
Treatment of chorea (2)

• Treat psychiatric symptoms
• Surgery – DBS ?which target (GPi, thalamus, STN); ?which frequency (60Hz, 130Hz)
• Transplantation – promising early results in HD?
• Non-medical; PT, OT, assistive devices, ST, swallowing, feeding, social work, genetic counseling
Thank you!