Approach to the patient with (non-HD) chorea

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Disclosures

- International Parkinson Disease and Movement Disorders Society
- International Association of Parkinsonism and Related Disorders
- Neurocrine Biosciences, Inc.
- Teladoc Health, Inc.

Learning objectives

By the end of this webinar you will be able to:

- recognise chorea
- discuss the differential diagnosis for the patient with chorea
- discuss the work up for the patient with chorea

Webinar outline

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

Key points

- Chorea can be due to a wide variety of disorders; there can be important clues to the diagnosis in a variety of areas
- Use of anti-psychotics may mask the diagnosis
- Precise diagnosis is critical for management and genetic counselling

Question 1

A. What is your professional background? (Single choice)
B. Neurologist
C. Neuropediatrician
D. Neurology resident
E. Psychiatrist
F. Nurse
G. Physiotherapist
H. Geneticist
I. Psychologist
J. Patient or patient representative
K. Other

What is chorea?

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

Evaluation of the patient with chorea

- Family history
- Time course
- Phenomenology
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- Other neurological features
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- Neuroimaging and laboratory work-up

A flow chart for the evaluation of chorea

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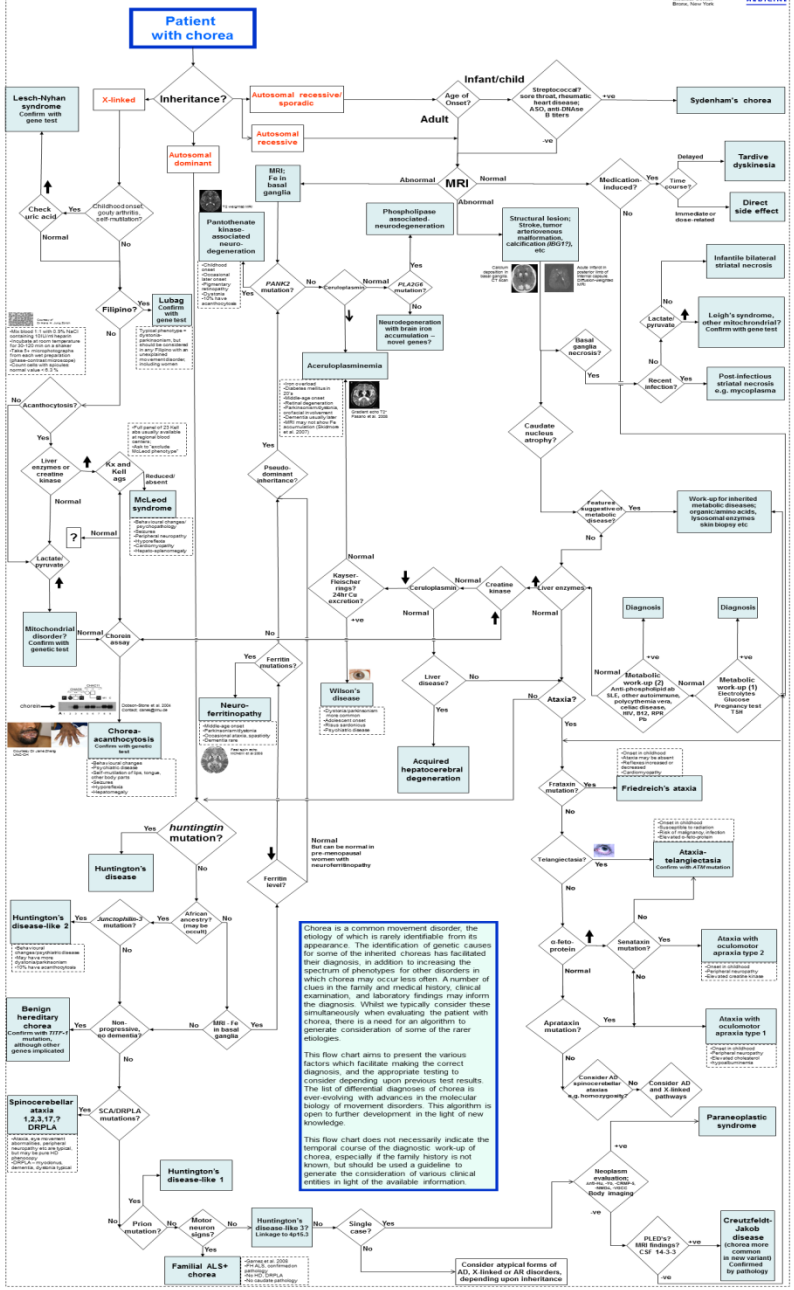

Evaluation of the patient with chorea

- **Family history/ethnic background**
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Family history positive

- Autosomal dominant
- Autosomal recessive
- X-linked
- Mitochondrial

Family history negative
- does not exclude genetic etiology

- Decreased penetrance
- Non-paternity
- Unknown parental medical history
- Parental death prior to disease manifestation
- Different parental phenotype
- *De novo* mutations
- Autosomal recessive disorders in small families

Chorea: autosomal dominant

- HD
- *C9orf72* expansions
- HDL1 (prion disease; single family)
- HDL2 (African ancestry)
- Spinocerebellar ataxias, esp. SCA 1, 2, 3, 8, 12, 17(=HDL4), 48
- Dentatorubropallidoluysian atrophy (mainly, but not exclusively, Japanese)
- Benign hereditary chorea
- Neuroferritinopathy (one of the NBIA disorders)
- “Fahr’s disease” - idiopathic basal ganglia calcification (*SLC20A2, PDGFRB, PDGFB*) and other loci
- Paroxysmal dyskinesias

C9orf72 disease

- Autosomal dominant
- Large hexanucleotide repeat expansions GGGGCC
- **Commonest cause** of familial and sporadic **ALS** and **frontotemporal dementia** in many populations
- A significant cause of huntingtonism in non-African European populations (2% in UK; 1/39 in Serbia; 2/40 Greece)
- **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

Huntington's Disease-like 2

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

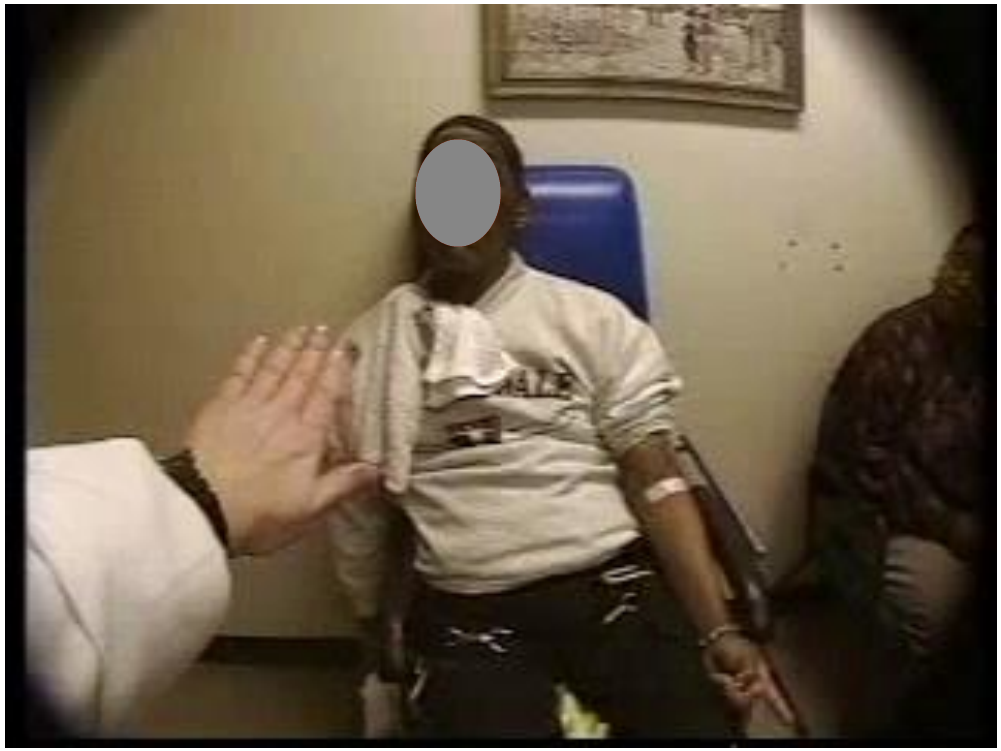
Russell L. Margolis, MD,[1,2] Elizabeth O'Hearn, MD,[3,4] Adam Rosenblatt, MD,[1] Virginia Willour, PhD,[1] Susan E. Holmes, PhD,[1] Mary L. Franz, MSW,[1] Colleen Callahan, BA,[1] Hyon S. Hwang, BA,[1] Juan C. Troncoso, MD,[3,5] and Christopher A. Ross, MD, PhD[1,2,4]

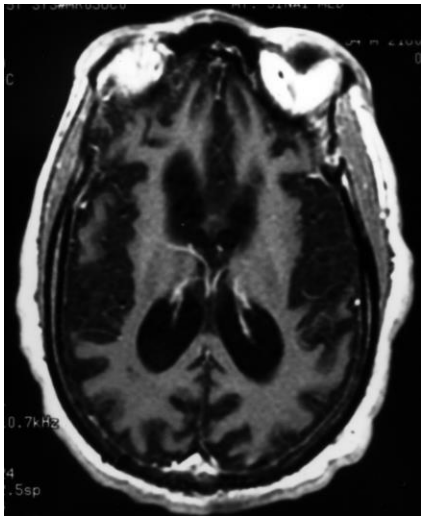
Ann Neurol 2001;50:373–380

- 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

Huntington's disease-like 2

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





Huntington's disease-like 2
Parkinsonian phenotype

- Nephew of proband
- mother=obligate carrier - died aged 25
- Onset aged 28
- 38 at examination

Courtesy of Dr J. Jankovic

X-linked

- Filipino males - Lubag (DYT3), island of Panay, Capiz province
- Lesch-Nyhan (childhood, self-mutilation)
- McLeod syndrome
- FXTAS

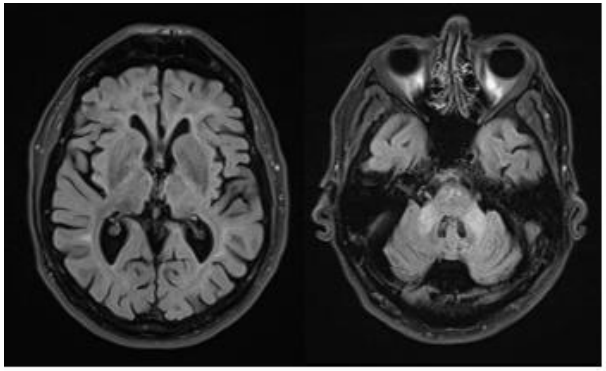

Movement Disorders

CASE REPORT

CLINICAL PRACTICE

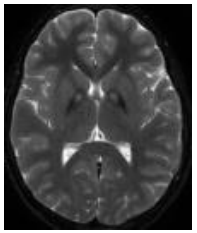
A Case of Generalized Chorea Presenting as an Early Feature of Fragile-X Associated Tremor/Ataxia Syndrome

Fariha Islam, FRACP, MBBS, BPsych. (Hons)* and Will Lee, FRACP, MBBS, D.Med.Sc.



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
- Niemann-Pick C
- Infantile bilateral striatal necrosis
- HDL3 - (Kambouris et al '00) (one family)
- Other pediatric metabolic disorders (glutaric aciduria….)



Niemann-Pick C

Usually ataxia, but also parkinsonism (PSP-like), dystonia, rarely chorea

Niemann Pick Type C as Presentation of Huntington-Like Syndrome

Lucia Zavala, Sergio Rodriguez Quiroga, Patricia Vega, Nancy Medina, Dolores González Morón, Nélida Garretto, Tomoko Arakaki, Marcelo Kauffman (Buenos Aires, Argentina)

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Evaluation of the patient with chorea

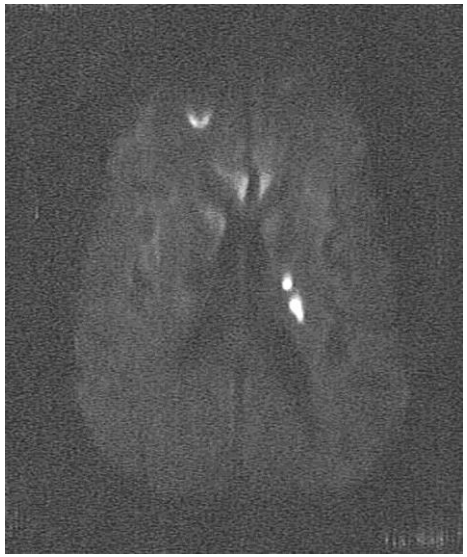
- Family history
- **Time course**
- Phenomenology
- Exacerbating/relieving factors
- Other neurological features
- Other medical conditions
- Medications
- Neuroimaging and laboratory work-up

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



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- **Phenomenology**
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Phenomenology of chorea

- **Distribution** – orofacial (tardive dyskinesia, chorea-acanthocytosis, acquired hepatocerebral degeneration)
  - trunk, neck, limbs

Acquired hepatocerebral degeneration

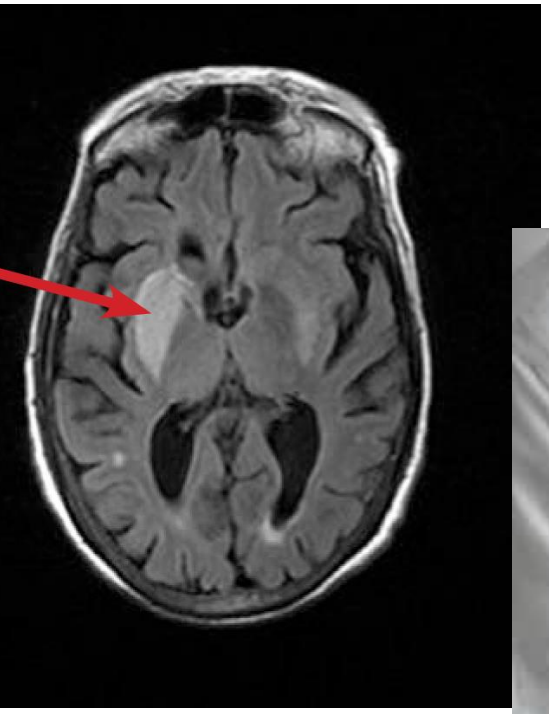
- Hepatic failure following viral hepatitis
- Awaiting liver transplantation

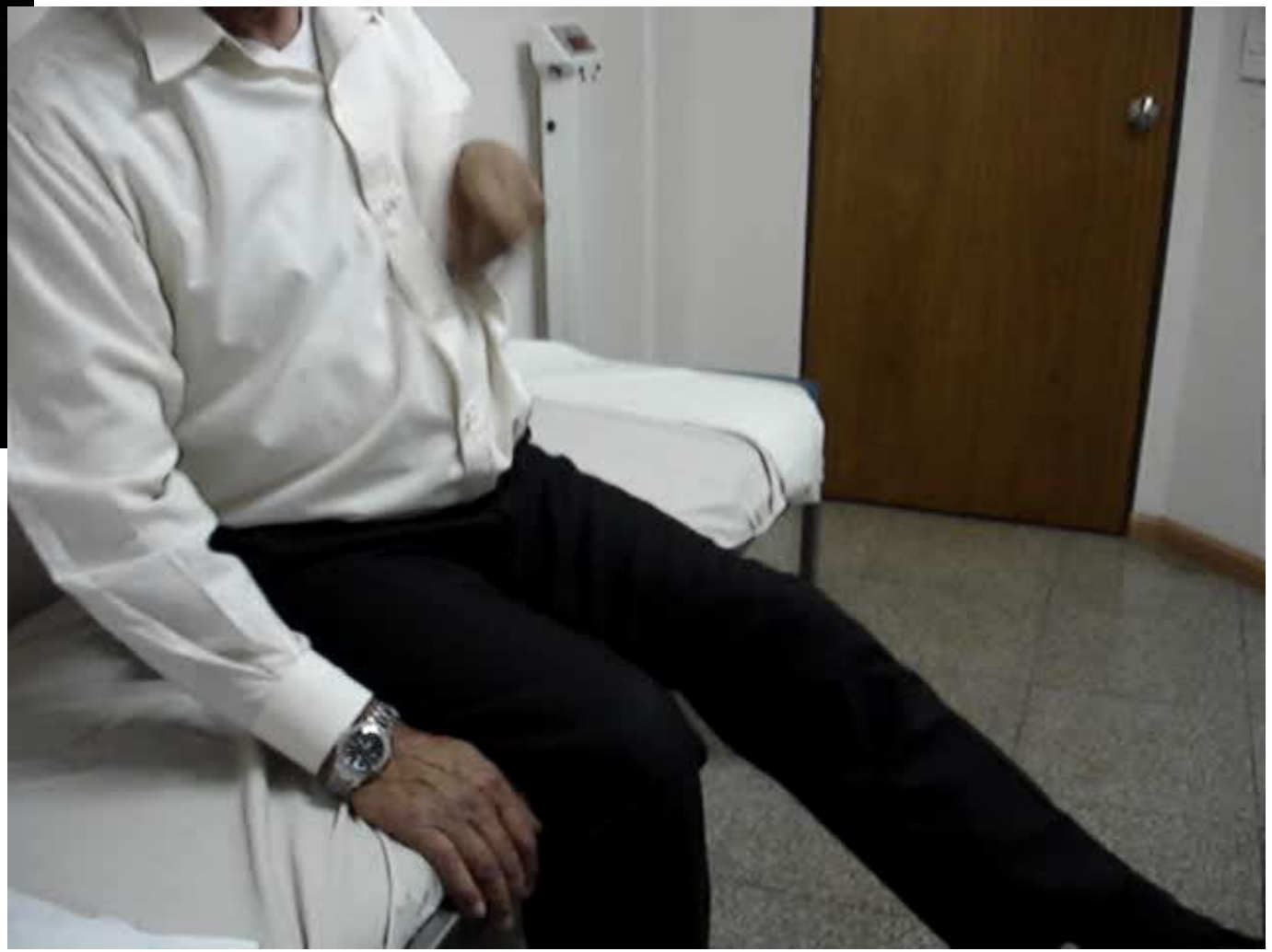
Courtesy of John C. Morgan, MD, PhD., and Kapil Sethi, MD, FRCP(UK), Augusta, Georgia

Asymmetric chorea: structural/metabolic causes

- Cerebral palsy
- Post-pump chorea (pediatric, rarely adult)
- Stroke
- Other vascular; AVM, vasculitides, moya-moya, cavernous angioma
- Tumour
- Multiple sclerosis
- Diabetic non-ketotic hyperglycemia
- Autoimmune
- Polycythemia rubra vera

Hemichorea in diabetic non-ketotic hyperglycemia





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
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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, 8, 12, 17, 48); DRPLA; AR ataxias**
- 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, 8,12, 17, 48); DRPLA; autosomal recessive ataxias - ataxia telangiectasia, ataxia with oculomotor apraxias
- **Decreased reflexes – chorea-acanthocytosis, McLeod syndrome,** SCAs
- **Seizures – chorea-acanthocytosis, McLeod syndrome**

Question 2

Have you seen a patient with chorea-acanthocytosis or McLeod syndrome?

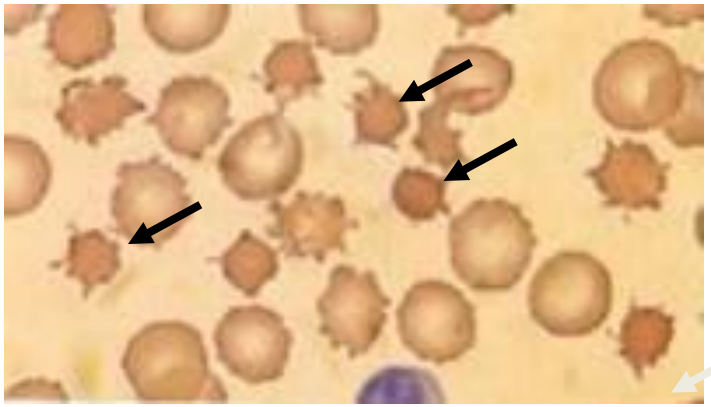
A. Yes, both
B. Yes, chorea-acanthocytosis
C. Yes, McLeod syndrome
D. Maybe – I'm not sure
E. No

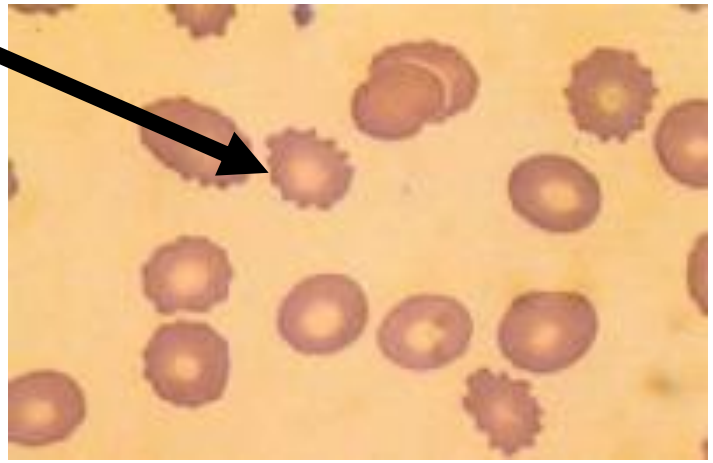
Chorea-acanthocytosis
(VPS13A disease)

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

Acanthocytosis

- Variably present for reasons which are unclear
- Membranes can 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**





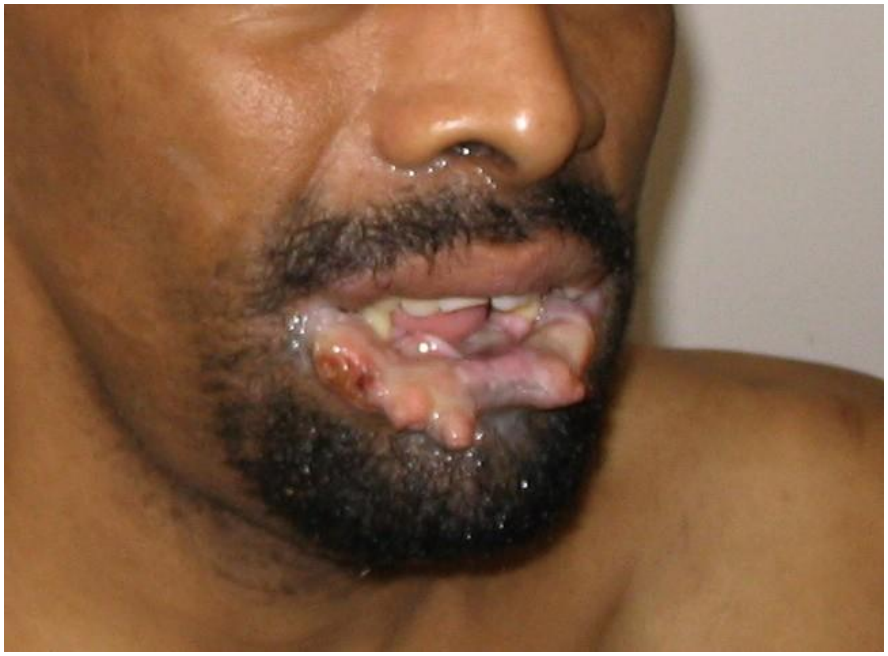
Chorea-acanthocytosis

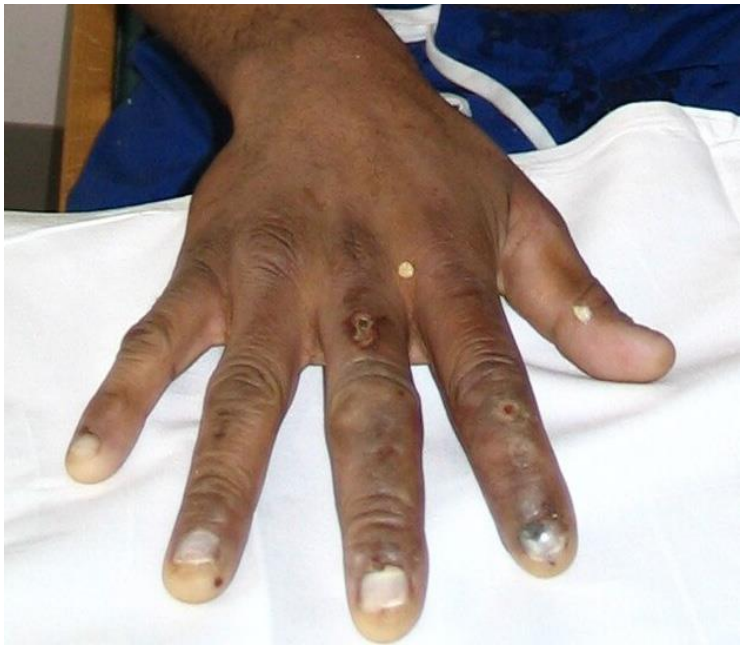
- 31 y/o man with gait difficulty
- No family history
- Developed psychotic depression aged 20
- Gait difficulty and involuntary movements for 3 years
- One seizure
- Distal sensory loss
- Tics (vocal), dropping things
- Head pulls to right
- Occasional falls
- Weight loss
- Problems with eating
- Forgetfulness, 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)

Performed by Dr Benedikt Bader, Munich

Orofacial dyskinesia, self-mutilation in chorea-acanthocytosis





Courtesy Dr Jane Zheng, UNC-CH

McLeod syndrome

(X-linked neuroacanthocytosis)

- Poor hygiene noted aged 42; at 48 unable to perform simple work tasks
- Weight loss
- Decreased peripheral sensation, decreased reflexes
- Elevated LFTs, CK
- underwent liver biopsy, bone marrow as part of work up
- + acanthocytosis
- CT – bilateral caudate atrophy

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**

Question 3

Which of the following is a useful clue to the diagnosis of a neuroacanthocytosis syndrome?

A. Elevated CK
B. Weight gain
C. History of affected parent
D. Abnormal ceruloplasmin

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- Family history
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- Other neurological features
- **Other medical conditions**
- Medications
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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/CV2, anti-Yo, anti-CASPR, anti-GAD65, anti-NMDA receptor, anti-LG1-1, anti-striational?.....)
- Non-paraneoplastic; anti-LGI-1, anti-CASPR….
- 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

Coeliac-associated chorea

•Compliance with gluten-free diet – reduced movements, reduced anti-gliadin abs

Evaluation of the patient with chorea

- Family history
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- Other neurological features
- Other medical conditions
- **Medications**
- Neuroimaging and laboratory work-up

Chorea: drug-induced

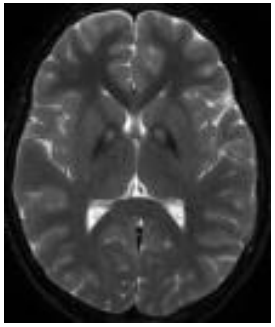
- Levo-dopa-induced dyskinesia in Parkinson's disease (peak dose; on-off)
- Direct drug effect; cocaine, amphetamine, anticonvulsants, Li, and other stimulants
- Estrogens (oral contraceptives, hormone replacement therapy) – may worsen underlying condition e.g. chorea-acanthocytosis
- Tardive (typical and atypical neuroleptics, anti-convulsants?, Li?, SSRIs?)
- Use of anti-psychotics for psychiatric symptoms may mask appreciation of movement disorder due to neurodegenerative etiology (HD, *C9ORF72*, HDL2, chorea-acanthocytosis, McLeod)

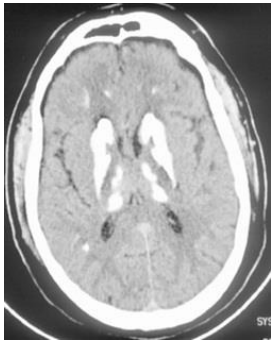
Evaluation of the patient with chorea

- 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**





Laboratory evaluation of the patient with chorea

- Routine blood chemistry (including liver enzymes), creatine kinase
- Thyroid function tests
- ASO, anti-DNAse B
- ESR, ANA, RhF, ANCA, anti-cardiolipin (anti-phospholipid) abs, Sjogren's…
- Anti-gliadin abs
- RPR
- B12/folate
- CBC, peripheral blood smear (acanthocytosis)
- Alpha-feto-protein
- Pregnancy test
- HIV
- Ceruloplasmin, ferritin
- Chorein Western blot
- McLeod phenotype (Kx and Kell ag expression)
- Genetic testing - HD, HDL2, SCA 1, 2, 3, 8, 12, 17, 48, DRPLA, FXTAS, Friedreich's ataxia…….
- Whole exome sequencing
- Paraneoplastic markers – anti-CRMP5/CV2, anti-Hu, anti-Yo, anti-Ma, anti-NMDA receptors, anti-GAD65, anti-LGI1….

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- Family history
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Question 4

Which of the following can be a cause of chorea? (multiple answers)

A. Spinocerebellar ataxias
B. Huntington's disease-like 2
C. Senile chorea
D. Parkinson's disease medications
E. Anti-psychotic medications

Thank you!