A flow chart for the evaluation of chorea

Ruth H. Walker, MB., Ch.B., Ph.D.
Departments of Neurology, James J. Peters Veterans Affairs Medical Center, Bronx, NY, and Mount Sinai School of Medicine, New York, NY
ruth.walker@mssm.edu

Patient with chorea

Inheritance?

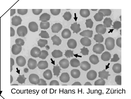
- **X-linked**
- **Autosomal recessive**
- **Autosomal dominant**
- **Autosomal recessive/sporadic**

Lesch-Nyhan syndrome
Confirm with gene test

Check uric acid
- Yes → **Childhood onset, gouty arthritis, self-mutilation?** → Yes
- Normal
- No

Acanthocytosis?
- No → **Filipino?** → Yes → **Lubag** Confirm with gene test
  - Typical phenotype = dystonia-parkinsonism, but should be considered in any Filipino with an unexplained movement disorder, including women
- Yes

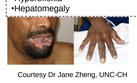
•Mix blood 1:1 with 0.9% NaCl containing 10IU/ml heparin
•Incubate at room temperature for 30-120 min on a shaker
•Take 5+ microphotographs from each wet preparation (phase-contrast microscope)
•Count cells with spicules: normal value < 6.3 %


Courtesy of Dr Hans H. Jung, Zürich

Liver enzymes or creatine kinase
- Normal
- Normal → **Lactate/ pyruvate**
  - Normal → **Mitochondrial disorder?** Confirm with gene test
  - Normal → **Chorein assay**
    - Normal → **?**
    - Normal → **Kx and Kell ags**
      - •Full panel of 23 Kell abs usually available at regional blood centers;
        •Ask to "exclude McLeod phenotype"
      - **McLeod syndrome**
        •Behavioural changes/ psychopathology
        •Seizures
        •Peripheral neuropathy
        •Hyporeflexia
        •Cardiomyopathy
        •Hepatosplenomegaly

Dobson-Stone et al. 2004
Contact – danek@imu.de

Chorea-acanthocytosis
Confirm with gene test
- •Behavioural changes/psychiatric disease
  •Self-mutilation of lips, tongue, other body parts
  •Seizures
  •Hyporeflexia
  •Hepatomegaly


Courtesy Dr Jane Zheng, UNC-CH

Huntington's disease
- Yes ← ***huntingtin* mutation?**
- No → ***C9ORF2* mutation?**
  - Yes → ***C9ORF72* disease**
    - •Variable phenotype
      •Often upper motor neuron signs
      •Reduced penetrance
      •Variable age of onset
  - No → **African ancestry? (may be occult)**
    - Yes → ***Junctophilin-3* mutation?**
      - Yes → **Huntington's disease-like 2**
        - •Behavioural changes/psychiatric disease
          •May have more dystonia/parkinsonism?
          •10% have acanthocytosis
      - No → **SCA/DRPLA mutations?**
        - Yes → **Spinocerebellar ataxia 1,2,3,8,12,17, DRPLA?**
          - •Ataxia, eye movement abormalities, peripheral neuropathy etc are typical, but may be pure HD phenocopy
            •DRPLA – myoclonus, dementia, dystonia typical
        - No → **Non-progressive, no dementia?**
          - Yes → **Hypotonia, Hyperreflexia, Facial movements, Paroxysmal/fluctuating movements?**
            - Yes → **ADCY-5 dyskinesia** Adenylate cyclase-5 mutation
              - No → **Benign hereditary chorea** *NKX2.1 (TITF-1)* mutation
              - No
            - No → **Thyroid, pulmonary, involvement?**
          - No → **Prion mutation?**
            - Yes → **Single case?**
              - Yes → **Creutzfeldt-Jakob disease** (chorea more common in new variant) Confirmed by pathology
              - No → **CACNA1A mutation?**
                - No → **Consider atypical forms of AD, X-linked or AR disorders, depending upon inheritance**
            - No → **Other FTD syndrome? VCP, FUS, UBQLN2**
          - Yes → **Huntington's disease-like 1?**

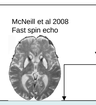
Pantothenate kinase-associated neurodegeneration
- •Childhood onset
  •Occasional later onset
  •Pigmentary retinopathy
  •Dystonia
  •10% have acanthocytosis

MRI; Fe in basal ganglia ?
- Yes → ***PANK2* mutation?**
  - Yes → **Pseudo-dominant inheritance?**
    - Yes → **Neuroferritinopathy**
      - •Middle-age onset
        •Parkinsonism/dystonia
        •Occasional ataxia, spasticity
        •Dementia rare
    - No → **Ferritin mutations?**
      - Yes → **Neuroferritinopathy**
      - No → **Ferritin level?**
        - **Normal** But can be normal in pre-menopausal women with neuroferritinopathy
        - **Iron in basal ganglia?**
          - **White matter lesions?**
            - **Cryopyrin-associated periodic syndrome?**
              - •Deafness
                •Elevated anti-cardiolipin IgG
                •Mutation of NLPR3
            - **Non-diagnostic** → **MRI**
  - No → **Ceruloplasmin?**
    - Normal → ***PLA2G6* mutation?**
      - Yes → **Phospholipase-associated neurodegeneration**
      - No → **Other neurodegeneration with brain iron Accumulation disorder… FAHN, MPAN, BPAN…**
    - **Aceruloplasminemia**


Fasano et al. 2008
Gradient echo T2*

- •iron overload
  •Diabetes mellitus in 20's (from pancreatic iron)
  •Middle-age onset
  •Retinal degeneration (from iron deposition)
  •Parkinsonism/dystonia, orofacial involvement is typical
  •Dementia usually later
  •MRI may not show Fe accumulation (Skidmore et al. 2007)

PKAN: T2 weighted MRI


McNeill et al 2008
Fast spin echo

Kayser-Fleischer rings? 24hr Cu excretion?
- Normal → **Ceruloplasmin?**
  - Normal → **Creatine kinase**
    - Normal → **Liver enzymes**
      - Normal → **Recent liver disease?**
        - No → **Ataxia?**
          - No → **Acquired hepatocerebral degeneration**
          - Yes → **Frataxin mutation?**
            - Yes → **Friedreich's ataxia**
              - •Onset in childhood
                •Ataxia may be absent
                •Reflexes increased or decreased
                •Cardiomyopathy
            - No → **Telangiectasia?**
              - Yes → **Ataxia-telangiectasia** Confirm with *ATM* mutation


- •Onset in childhood
  •Susceptible to radiation
  •Risk of malignancy, infection
  •Elevated α-feto-protein

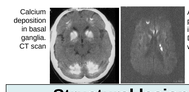
- No → **α-feto-protein**
  - Normal → **Aprataxin mutation?**
    - Yes → **Ataxia with oculomotor apraxia type 1**
      - •Onset in childhood
        •Peripheral neuropathy
        •Elevated cholesterol
        •hypoalburninemia
    - No → **Consider AD spinocerebellar ataxias e.g. homozygosity?**
      - **Consider AD and X-linked pathways**
  - No → **Senataxin mutation?**
    - Yes → **Ataxia with oculomotor apraxia type 2**
      - •Onset in childhood
        •Peripheral neuropathy
        •Elevated creatine kinase
    - No

- Yes → **Ceruloplasmin?**
  - Normal → **Gordon Holmes syndrome/ *RNF216* mutations?**
    - •hypogonadism
      •dementia
      •ataxia
  - +ve → **Wilson's disease**
    - •Dystonia/parkinsonism/dystonia more common
      •Adolescent onset
      •Risus sardonicus
      •Psychiatric disease

Normal

Age of Onset?
- Infant/child → **Streptococcal? sore throat, rheumatic heart disease ASO, anti-DNAse B titers**
  - +ve → **Sydenham's chorea**
  - Normal
- Adult

MRI
- normal
- **Structural lesion;** Stroke, tumor arteriovenous malformation, calcification *(SLC20A2, PDGFRB, PDGFB, XPR1?)*, etc


Calcium deposition in basal ganglia, CT scan

Acute infarct in posterior limb of internal capsule. Diffusion-weighted MRI

Medication-induced?
- Yes → **Time course?**
  - Immediate or dose related → **Direct side effect**
  - Delayed → **Tardive dyskinesia**
- No

Lactate/ pyruvate
- No → **Infantile bilateral striatal necrosis; ?PDE10A mutations** (see review by Tonduti et al. 2016)
- No → **Leigh's syndrome, other mitochrondrial?** Confirm with gene test

Recent infection?
- Yes → **Post-infectious striatal necrosis**
- No

Basal ganglia necrosis?
- Yes
- No → **Caudate nucleus atrophy?**
  - Yes → **Features suggestive of metabolic disease?**
    - Yes → **Work-up for inherited metabolic diseases; organic/amino acids, lysosomal Enzymes, skin biopsy etc**
      - Negative
    - No

White matter lesions
- **GPR88 mutations?**
- No → **GNA01 mutations?**
  - •Childhood onset
    •Seizures (variable)
    •Delayed myelination or normal MRI

Liver enzymes
- Normal → **Diagnosis**
  - +ve → **Metabolic work-up (2) Anti-phospholipid ab SLE, other autoimmune Polycythemia vera Celiac disease HIV, B12, RPR Pb**
    - Normal → **Metabolic work-up (1) Electrolytes Glucose Pregnancy test TSH**
      - +ve → **Diagnosis**

Neoplasm evaluation; Anti-Hu, Yo, CRMP-5, GAD65 NMDA, VGCC Caspr2, LGI-1, striational ……..
- +ve → **Paraneoplastic syndrome**
  - Negative workup → **Autoimmune non-paraneoplastic syndrome**
- -ve → **PLED's? MRI findings? CSF 14-3-3**
  - +ve → **Creutzfeldt-Jakob disease** (chorea more common in new variant) Confirmed by pathology
  - -ve

Chorea is a common movement disorder, the etiology of which is rarely identifiable from its appearance. The identification of genetic causes for some of the inherited choreas has facilitated their diagnosis, in addition to increasing the spectrum of phenotypes for other disorders in which chorea may occur less often. A number of clues in the family and medical history, clinical examination, and laboratory findings may inform the diagnosis. Whilst we typically consider these simultaneously when evaluating the patient with chorea, there is a need for an algorithm to generate consideration of some of the rarer etiologies.

This flow chart aims to present the various factors which facilitate making the correct diagnosis, and the appropriate testing to consider depending upon previous test results. The list of differential diagnoses of chorea is ever-evolving with advances in the molecular biology of movement disorders. This algorithm which is open to further development in the light of new knowledge, and may indeed become somewhat obsolete as whole exome/genome sequencing becomes more available.

This flow chart does not necessarily indicate the temporal course of the diagnostic work-up of chorea, especially if the family history is not known, but should be used a guideline to generate the consideration of various clinical entities in light of the available information.